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FILE COVERS 1907 - 12 Feb 2009 VOL 150 ISS 7
FILE LAST UPDATED: 11 Feb 2009 (20090211/ED)

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reclassification data for the third quarter of 2008.

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This file contains CAS Registry Numbers for easy and accurate
substance identification.

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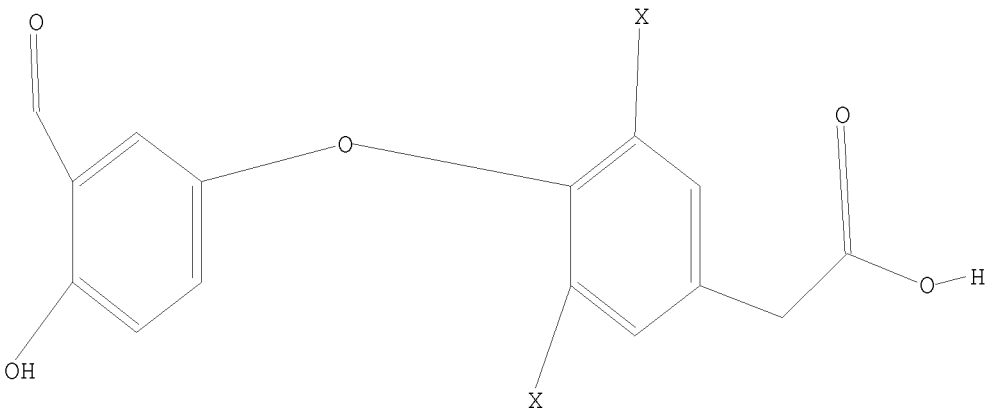

Structure attributes must be viewed using STN Express query preparation.

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L3 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:632256 CAPLUS
DOCUMENT NUMBER: 147:226220
TITLE: QSAR study of selective ligands for the thyroid hormone receptor β
AUTHOR(S): Liu, Huanxiang; Gramatica, Paola
CORPORATE SOURCE: QSAR Research Unit in Environmental Chemistry and Ecotoxicology, Department of Structural and Functional Biology, University of Insubria, Varese, 21100, Italy
SOURCE: Bioorganic & Medicinal Chemistry (2007), 15(15), 5251-5261
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this paper, an accurate and reliable QSAR model of 87 selective ligands for the thyroid hormone receptor β 1 (TRβ1) was developed, based on theor. mol. descriptors to predict the binding affinity of compds. with receptor. The structural characteristics of compds. were described wholly by a large amount of mol. structural descriptors calculated by DRAGON. Six most relevant structural descriptors to the studied activity were selected as the inputs of QSAR model by a robust optimization algorithm Genetic Algorithm. The built model was fully assessed by various validation methods, including internal and external validation, Y-randomization test, chemical applicability domain, and all the validations indicate that the QSAR model we proposed is robust and satisfactory. Thus, the built QSAR model can be used to fast and accurately predict the binding affinity of compds. (in the defined applicability domain) to TRβ1. At the same time, the model proposed could also identify and provide some insight into what structural features are related to the biol. activity of these compds. and provide some instruction for further designing the new selective ligands for TRβ1 with high activity.

IT 725239-20-3 725239-64-5 725239-65-6
725239-66-7 725239-67-8 725239-69-0
725239-70-3 725239-71-4 725239-72-5
725239-73-6 725239-74-7
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(QSAR of selective ligands for thyroid hormone receptor β)

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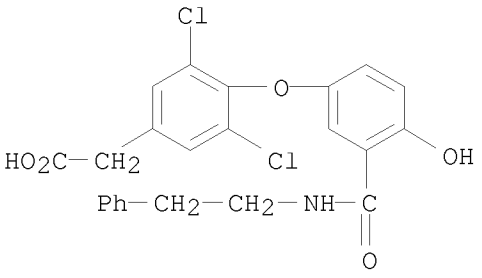

RN 725239-64-5 CAPLUS
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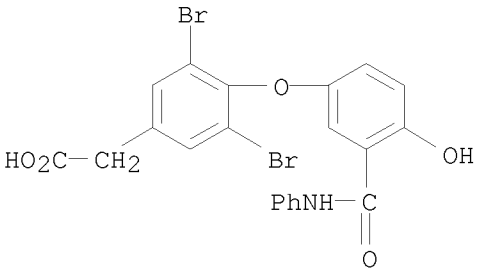

RN 725239-65-6 CAPLUS
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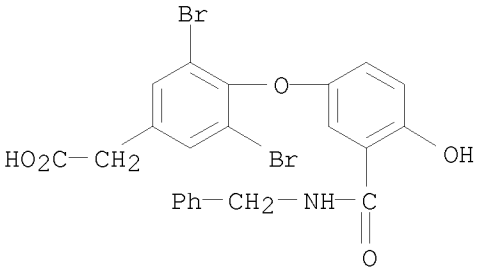

RN 725239-66-7 CAPLUS
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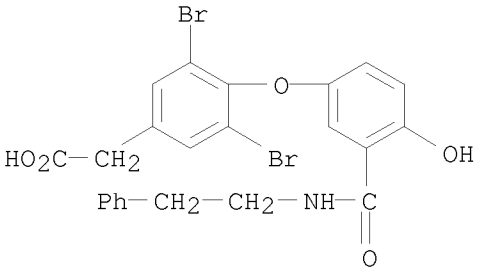

RN 725239-67-8 CAPLUS
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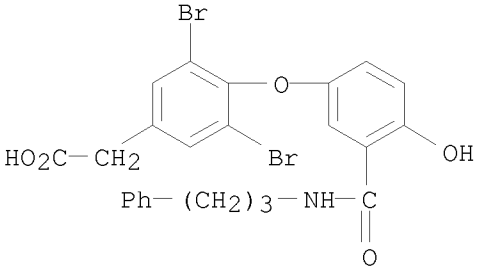

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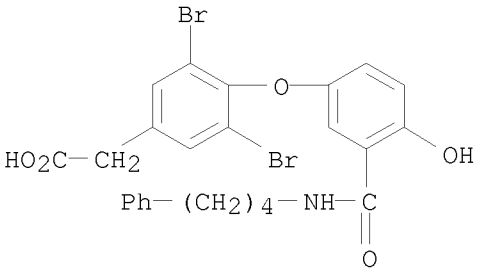

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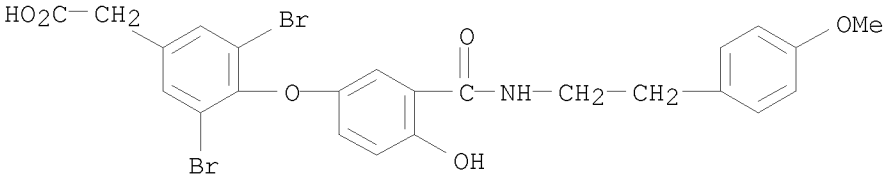

RN 725239-71-4 CAPLUS
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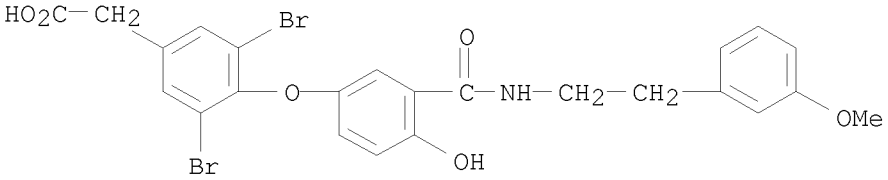

RN 725239-72-5 CAPLUS
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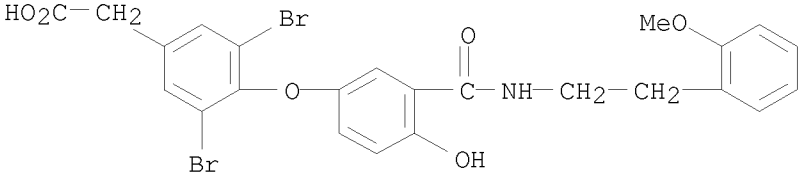

RN 725239-73-6 CAPLUS
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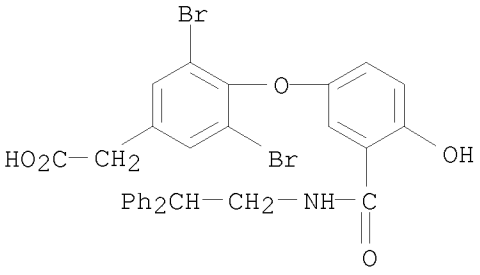

RN 725239-74-7 CAPLUS
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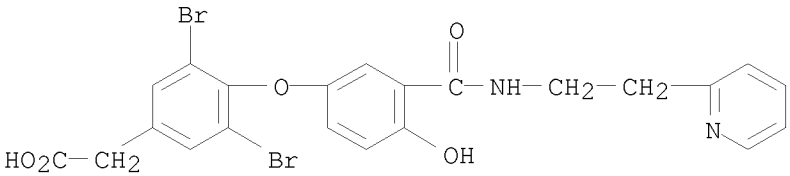
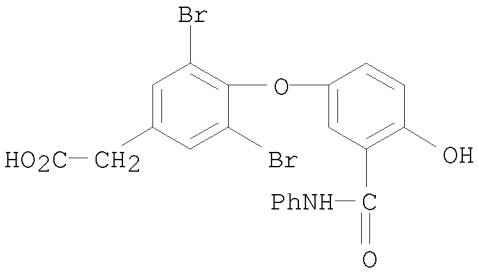


REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:590026 CAPLUS
DOCUMENT NUMBER: 147:226206
TITLE: 2D QSAR studies on thyroid hormone receptor ligands
AUTHOR(S): Valadares, Napoleao F.; Castilho, Marcelo S.; Polikarpov, Igor; Garratt, Richard C.
CORPORATE SOURCE: Departamento de Fisica e Informatica, Instituto de Fisica de Sao Carlos, Universidade de Sao Paulo, Sao Carlos-SP, 13560-970, Brazil
SOURCE: Bioorganic & Medicinal Chemistry (2007), 15(13), 4609-4617
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 2D QSAR studies were carried out for a series of 55 ligands for the Thyroid receptors, TRα and TRβ. Significant cross-validated correlation coeffs. (q 2 = 0.781 (TRα) and 0.693 (TRβ)) were obtained. The models' predictive abilities were proved more valuable than the classical 2D-QSAR, and were further investigated by an external test set of 13 compds. The predicted values are in good agreement with exptl. values, suggesting that the models could be useful in the design of novel, more potent TR ligands. Contribution map anal. identified a number of positions that are promising for the development of receptor isoform specific ligands.
IT 725239-64-5
RL: PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
(QSAR studies on thyroid hormone receptor ligands)
RN 725239-64-5 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[(phenylamino)carbonyl]phenoxy]- (CA INDEX NAME)



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:927006 CAPLUS
DOCUMENT NUMBER: 141:395288
TITLE: New [3,5-dihalo-4-(4-hydroxyphenoxy)phenyl]acetic acid derivatives useful as thyroid receptor ligands, and their preparation, pharmaceutical compositions, and methods of use
INVENTOR(S): Ryono, Dennis E.; Hangeland, Jon J.; Friends, Todd J.; Dejneka, Tamara; Devasthale, Pratik; Caringal, Yolanda V.; Zhang, Minsheng; Doweyko, Arthur M. P.; Malm, Johan; Sanin, Andrei
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004093799	A2	20041104	WO 2004-US11883	20040416
WO 2004093799	A3	20050224		
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RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 20050004184	A1	20050106	US 2004-826100	20040415
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OTHER SOURCE(S): MARPAT 141:395288
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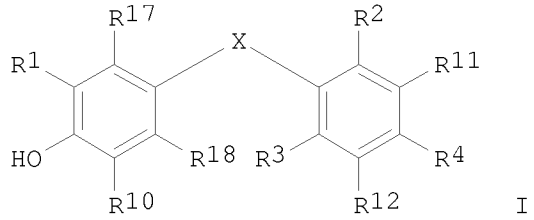

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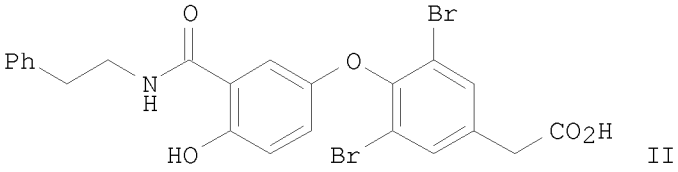

II

AB Thyroid receptor ligands are provided which have the general formula I [wherein: R1 = (un)substituted CONR5R6, CH2NR5R6, NR5COR6, OR7, R8, 4-R9-4,5-dihydrooxazol-2-yl; R2, R3 = H, halo, C1-4 alkyl or C3-5 cycloalkyl, provided that at least 1 of R2 and R3 ≠ H; R4 = (CH2)nR13 or (CH2)nCONR16CR13R14R15; R5, R6 = H, (hetero)aryl, (cyclo)alkyl, or (hetero)aralkyl; R7 = (hetero)aryl, alkyl, or (hetero)aralkyl; R8 = (hetero)aryl or cycloalkyl; R9 = R7 or H; R10 = H, halo, cyano, or alkyl; R11, R12 = H, halo, alkoxy, OH, cyano, or alkyl; R13 = COOH and esters, phosphonic and phosphinic acid and esters, sulfonic acid, tetrazole, hydroxamic acid, thiazolidinedione, acylsulfonamide, or other carboxylic acid surrogates; R14, R15 = H, alkyl; or R14R15 = (CH2)2-5, forming 3- to 6-membered cycloalkyl rings; R16 = H or C1-4 alkyl; R17 and R18 = H, halo, or alkyl; n = 0-4; X = O, S, S(O)2, S(O), Se, CO, NH, or CH2]. In addition, a method is provided for preventing, inhibiting or treating diseases or disorders associated with metabolism dysfunction, or which are dependent upon the expression of, a T3 regulated gene, wherein a compound I is administered therapeutically. Claims cover the above, as well as pharmaceutical compns. containing I, and methods of coadministration of I with other compds., particularly certain antidiabetic agents. Compds. I include selective agonists, partial agonists, antagonists, and partial antagonists of thyroid receptors (no data). Approx. 168 compds. were prepared For instance, Me (3,5-dibromo-4-hydroxyphenyl)acetate underwent O-arylation with (4-MeOC6H4)2I+ BF4-, and the resultant 4-methoxyphenyl ether derivative underwent a sequence of: (1) formylation in the 3-position, (2) O-demethylation, (3) oxidation of the aldehyde to an acid, (4) amidation of the acid, and (5) alkaline saponification of the ester, to give title compound II.

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725239-70-3P 725239-71-4P 725239-72-5P
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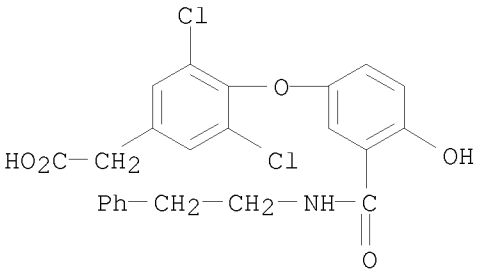
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of [dihalo(hydroxyphenoxy)phenyl]acetic acid derivs. as thyroid receptor ligands)

RN 725239-20-3 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[4-hydroxy-3-[[(2-phenylethyl)amino]carbonyl]phenoxy]- (CA INDEX NAME)



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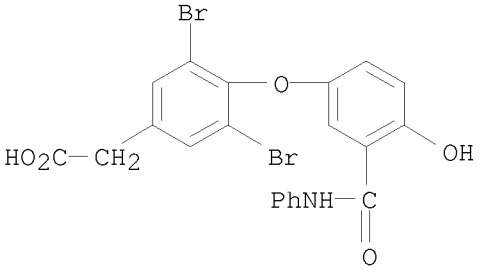
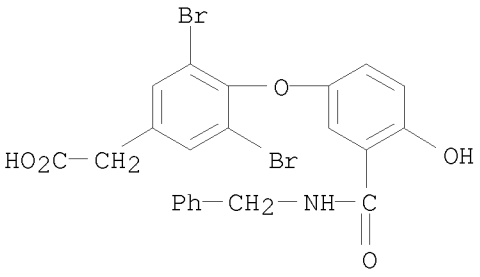
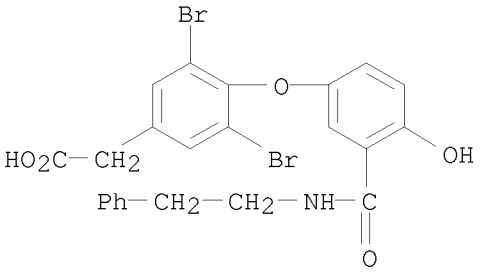


RN 725239-65-6 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[(phenylmethyl)amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 725239-66-7 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[(2-phenylethyl)amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 725239-67-8 CAPLUS
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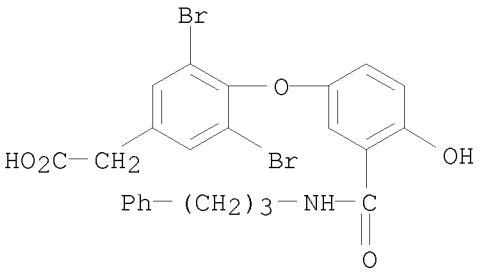

RN 725239-69-0 CAPLUS
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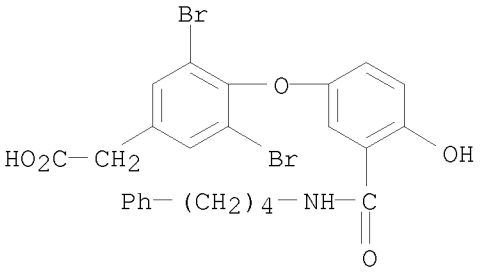

RN 725239-70-3 CAPLUS
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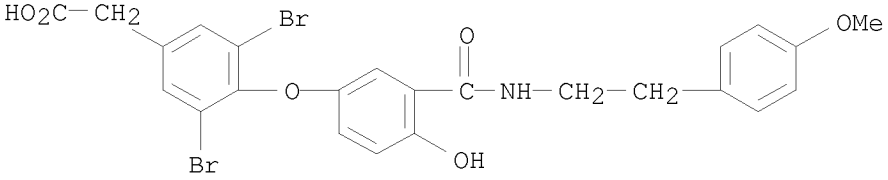

RN 725239-71-4 CAPLUS
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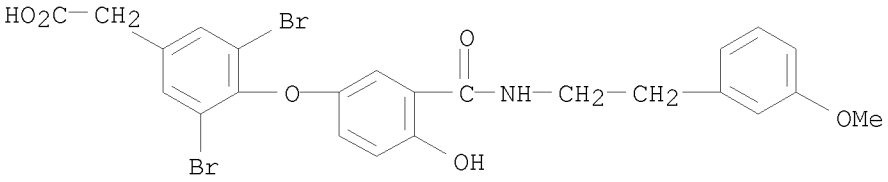

RN 725239-72-5 CAPLUS
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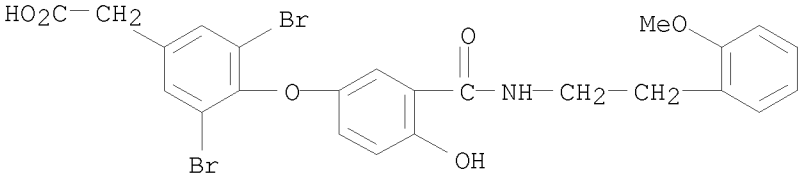

RN 725239-73-6 CAPLUS
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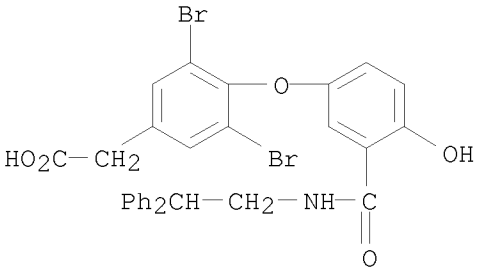
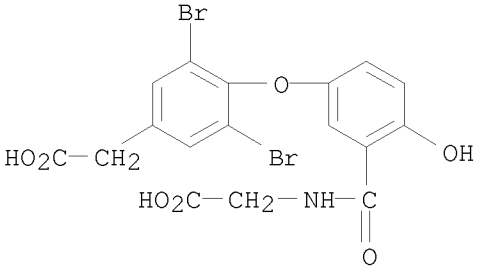
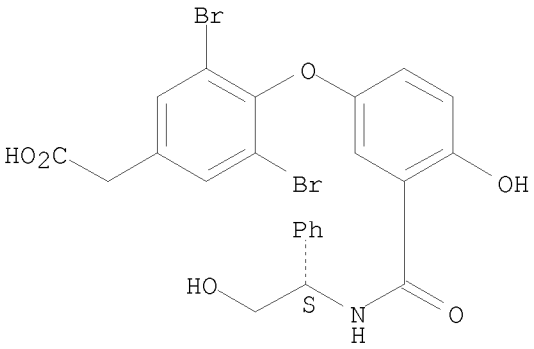


RN 788822-75-3 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[3-[[(carboxymethyl)amino]carbonyl]-4-hydroxyphenoxy]- (CA INDEX NAME)



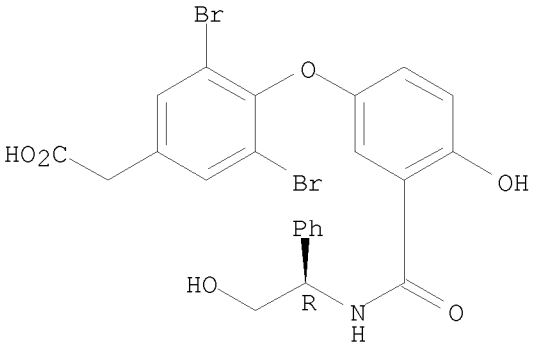
RN 788822-76-4 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1S)-2-hydroxy-1-phenylethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.



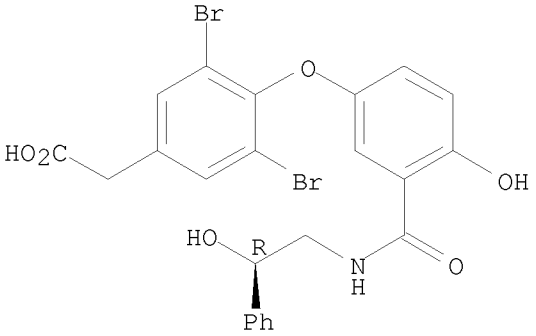
RN 788822-77-5 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1R)-2-hydroxy-1-phenylethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.



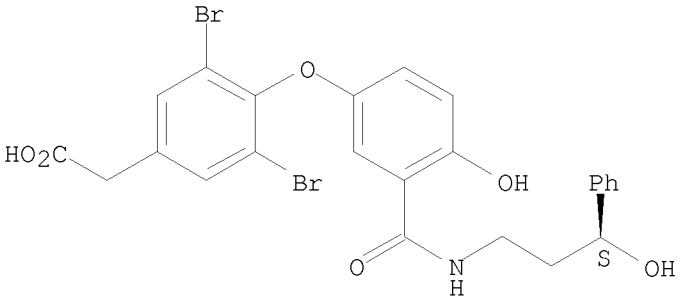
RN 788822-78-6 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(2R)-2-hydroxy-2-phenylethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.



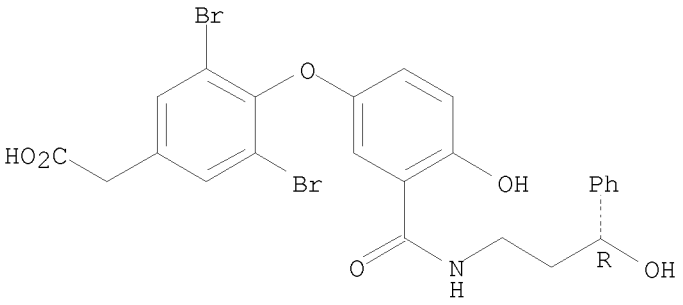
RN 788822-79-7 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(3S)-3-hydroxy-3-phenylpropyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.



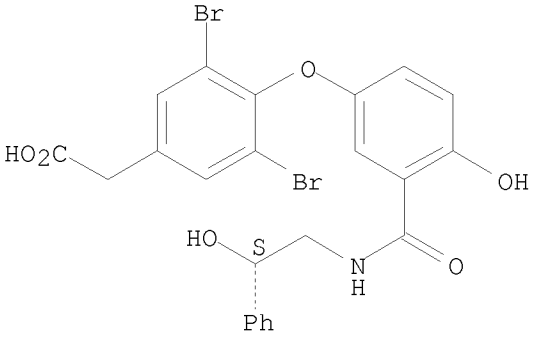
RN 788822-80-0 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(3R)-3-hydroxy-3-phenylpropyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.



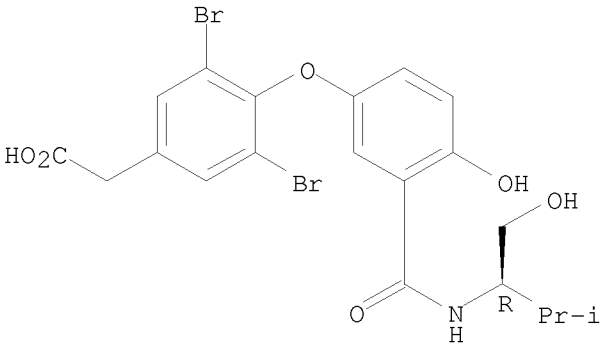
RN 788822-81-1 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(2S)-2-hydroxy-2-phenylethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.



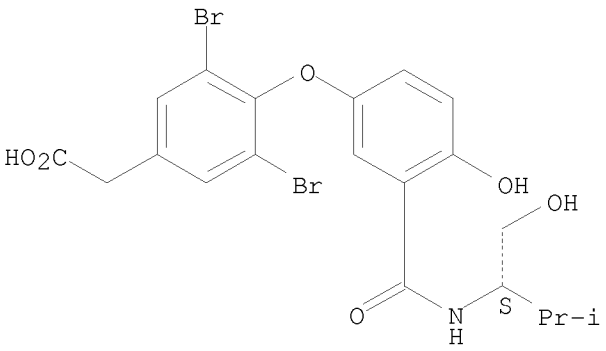
RN 788822-82-2 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1R)-1-(hydroxymethyl)-2-methylpropyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.



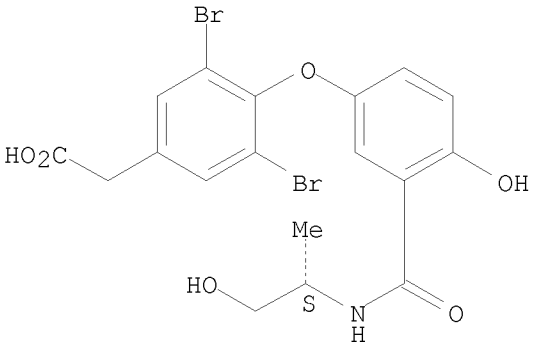
RN 788822-83-3 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1S)-1-(hydroxymethyl)-2-methylpropyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.



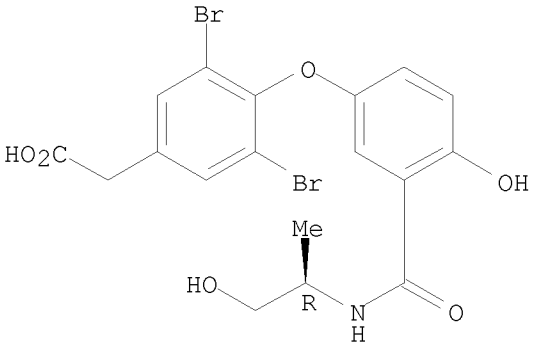
RN 788822-84-4 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1S)-2-hydroxy-1-methylethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.

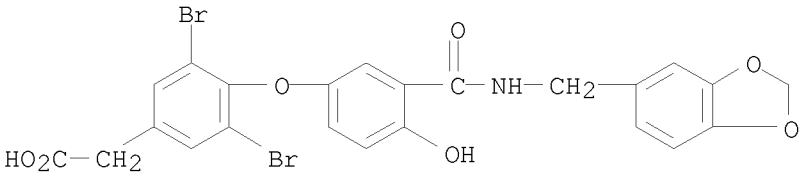


RN 788822-85-5 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1R)-2-hydroxy-1-methylethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

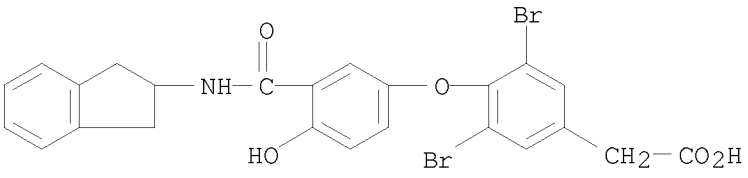
Absolute stereochemistry.



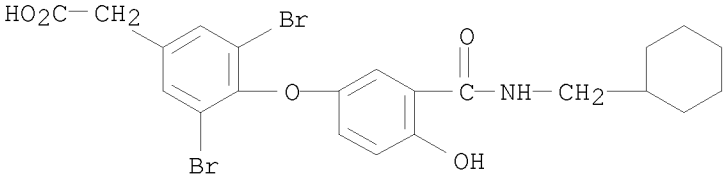
RN 788822-86-6 CAPLUS
CN Benzeneacetic acid, 4-[3-[[(1,3-benzodioxol-5-ylmethyl)amino]carbonyl]-4-hydroxyphenoxy]-3,5-dibromo- (CA INDEX NAME)



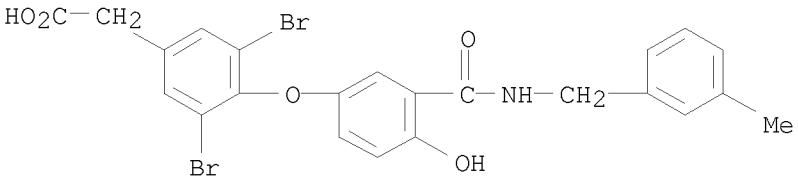
RN 788822-87-7 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[3-[[(2,3-dihydro-1H-inden-2-yl)amino]carbonyl]-4-hydroxyphenoxy]- (CA INDEX NAME)



RN 788822-88-8 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[3-[[(cyclohexylmethyl)amino]carbonyl]-4-hydroxyphenoxy]- (CA INDEX NAME)

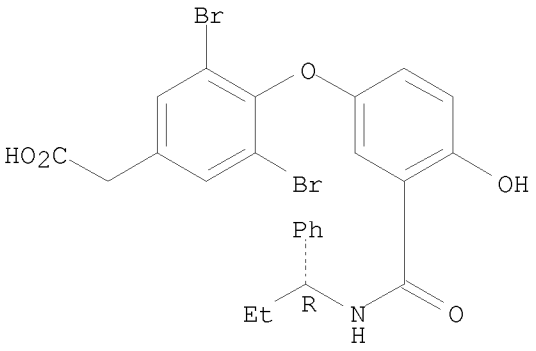


RN 788822-89-9 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(3-methylphenyl)methyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



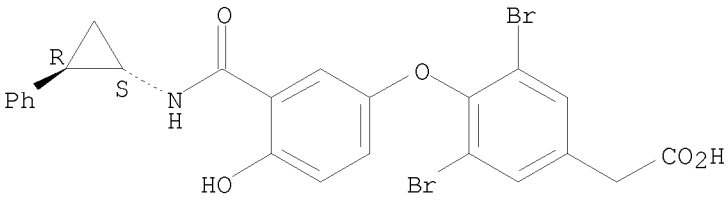
RN 788822-90-2 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1R)-1-phenylpropyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.



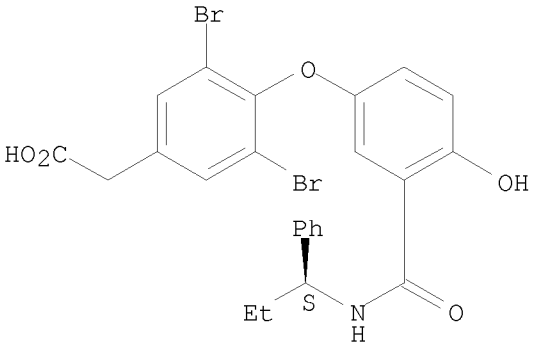
RN 788822-91-3 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1R,2S)-2-phenylcyclopropyl]amino]carbonyl]phenoxy]-, rel- (CA INDEX NAME)

Relative stereochemistry.

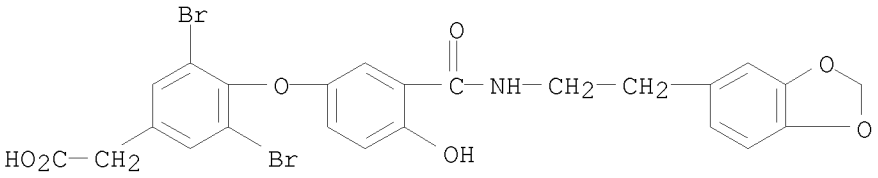


RN 788822-92-4 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1S)-1-phenylpropyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

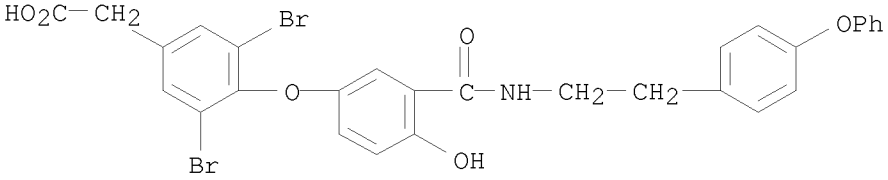
Absolute stereochemistry.



RN 788822-93-5 CAPLUS
CN Benzeneacetic acid, 4-[3-[[[2-(1,3-benzodioxol-5-yl)ethyl]amino]carbonyl]-4-hydroxyphenoxy]-3,5-dibromo- (CA INDEX NAME)

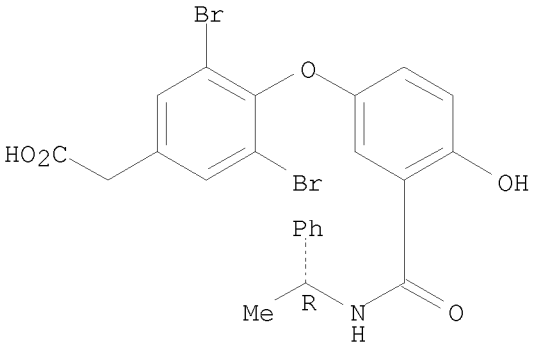


RN 788822-94-6 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[2-(4-phenoxyphenyl)ethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

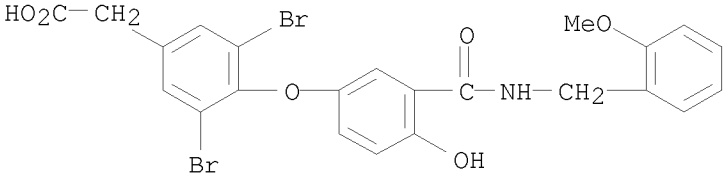


RN 788822-95-7 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1R)-1-phenylethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

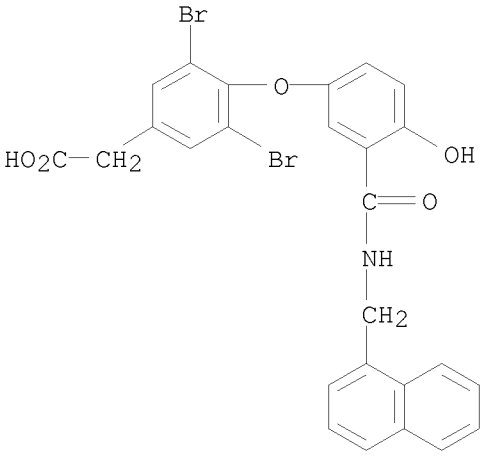
Absolute stereochemistry.



RN 788822-96-8 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(2-methoxyphenyl)methyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

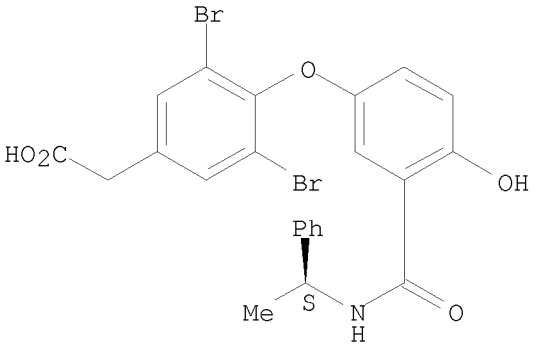


RN 788822-97-9 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[(1-naphthalenylmethyl)amino]carbonyl]phenoxy]- (CA INDEX NAME)

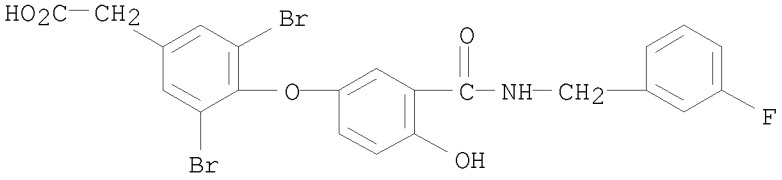


RN 788822-98-0 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1S)-1-phenylethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

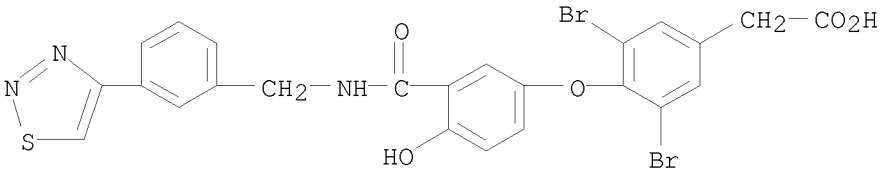
Absolute stereochemistry.



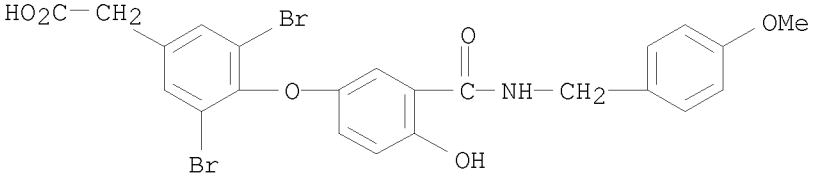
RN 788822-99-1 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[3-[[[(3-fluorophenyl)methyl]amino]carbonyl]-4-hydroxyphenoxy]- (CA INDEX NAME)



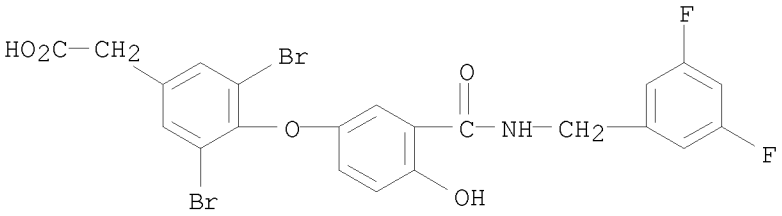
RN 788823-00-7 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[[3-(1,2,3-thiadiazol-4-yl)phenyl]methyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



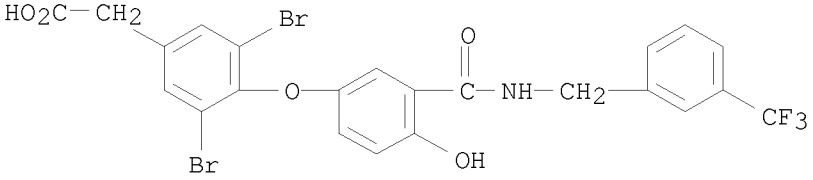
RN 788823-01-8 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(4-methoxyphenyl)methyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



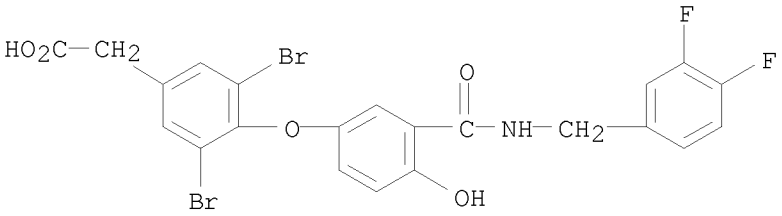
RN 788823-02-9 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[3-[[[(3,5-difluorophenyl)methyl]amino]carbonyl]-4-hydroxyphenoxy]- (CA INDEX NAME)



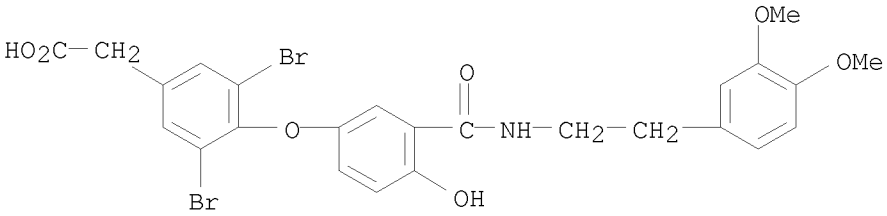
RN 788823-03-0 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[[3-(trifluoromethyl)phenyl]methyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 788823-04-1 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[3-[[[(3,4-difluorophenyl)methyl]amino]carbonyl]-4-hydroxyphenoxy]- (CA INDEX NAME)

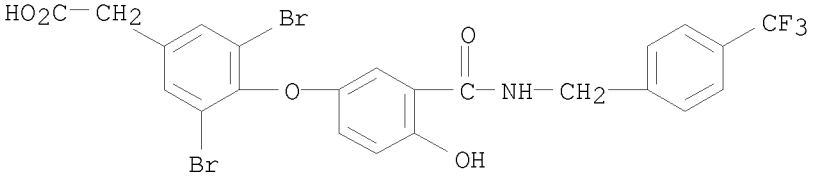


RN 788823-05-2 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[3-[[[2-(3,4-dimethoxyphenyl)ethyl]amino]carbonyl]-4-hydroxyphenoxy]- (CA INDEX NAME)

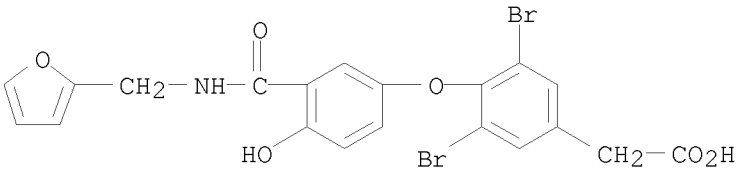


RN 788823-06-3 CAPLUS

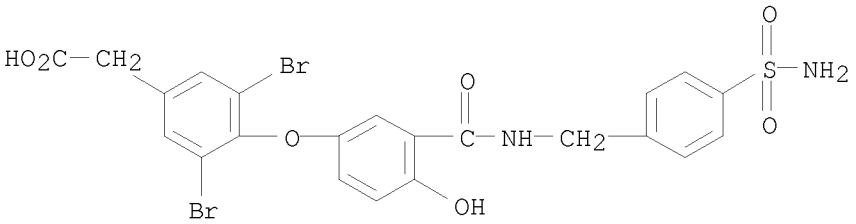
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[[4-(trifluoromethyl)phenyl]methyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



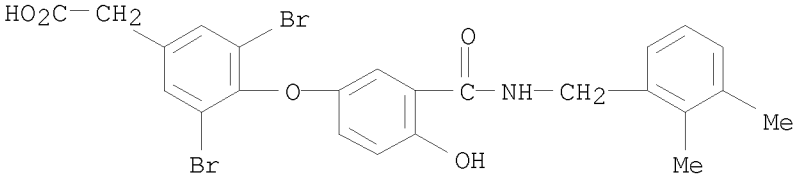
RN 788823-07-4 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[3-[[(2-furanylmethyl)amino]carbonyl]-4-hydroxyphenoxy]- (CA INDEX NAME)



RN 788823-08-5 CAPLUS
CN Benzeneacetic acid, 4-[3-[[[[4-(aminosulfonyl)phenyl]methyl]amino]carbonyl]-4-hydroxyphenoxy]-3,5-dibromo- (CA INDEX NAME)

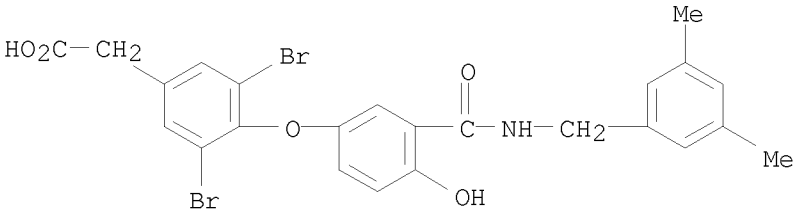


RN 788823-09-6 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[3-[[[(2,3-dimethylphenyl)methyl]amino]carbonyl]-4-hydroxyphenoxy]- (CA INDEX NAME)

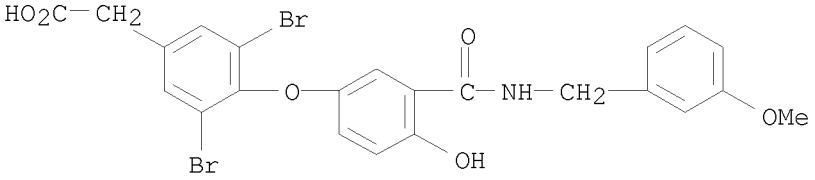


RN 788823-10-9 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[3-[[[(3,5-

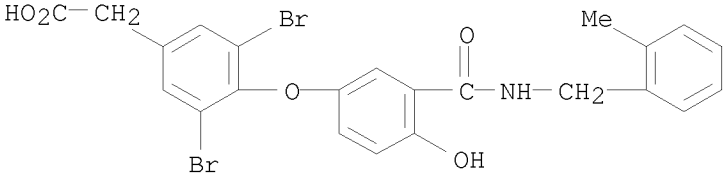
dimethylphenyl)methyl]amino]carbonyl]-4-hydroxyphenoxy]- (CA INDEX NAME)



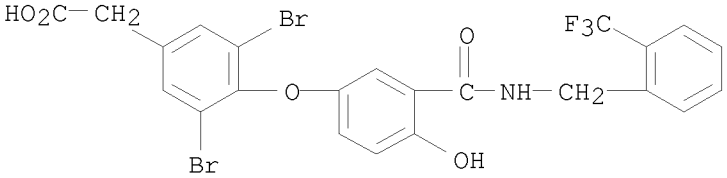
RN 788823-11-0 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(3-methoxyphenyl)methyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



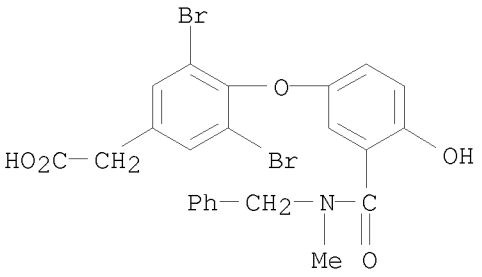
RN 788823-12-1 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(2-methylphenyl)methyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



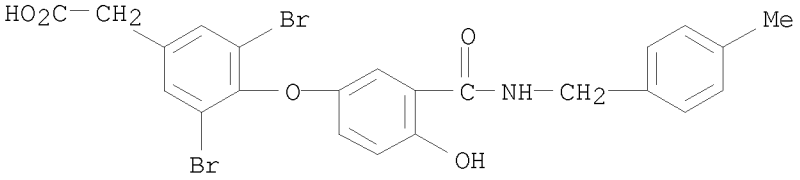
RN 788823-13-2 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[[2-(trifluoromethyl)phenyl]methyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 788823-14-3 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[methyl(phenylmethyl)amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 788823-15-4 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(4-methylphenyl)methyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 788823-16-5 CAPLUS
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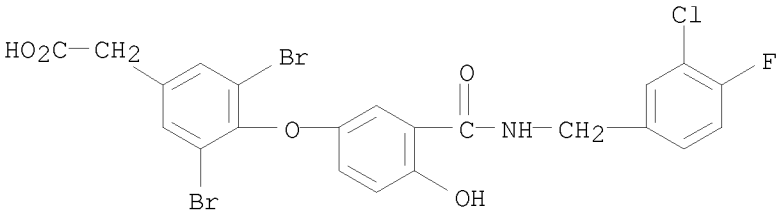

RN 788823-17-6 CAPLUS
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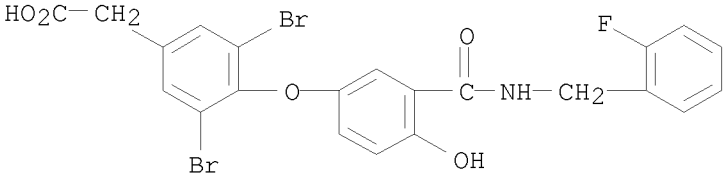

RN 788823-18-7 CAPLUS
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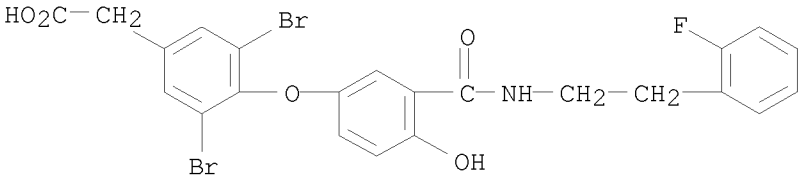

RN 788823-19-8 CAPLUS
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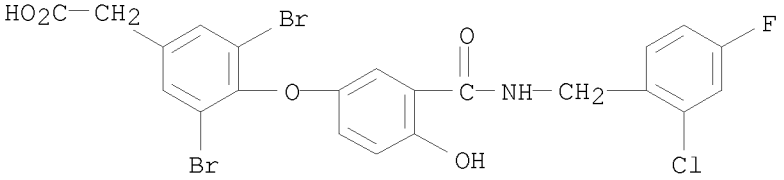

RN 788823-20-1 CAPLUS
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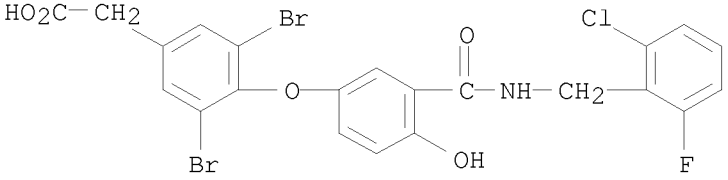

RN 788823-21-2 CAPLUS
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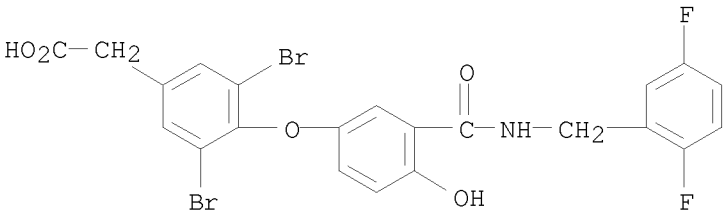

RN 788823-22-3 CAPLUS
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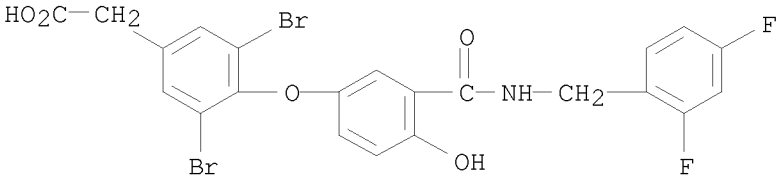

RN 788823-23-4 CAPLUS
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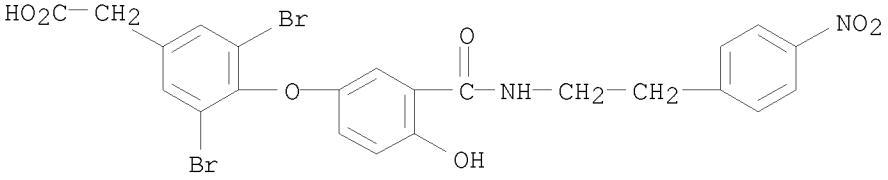

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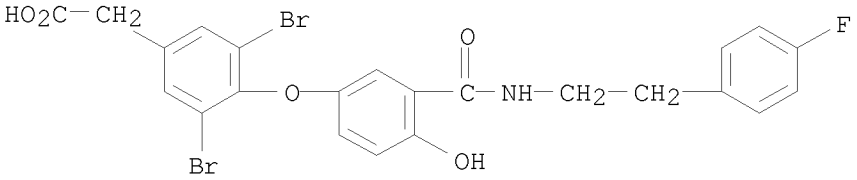

RN 788823-25-6 CAPLUS
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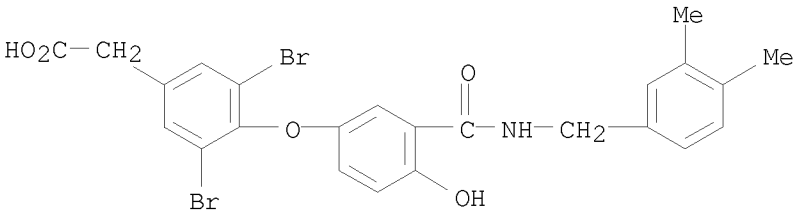

RN 788823-26-7 CAPLUS
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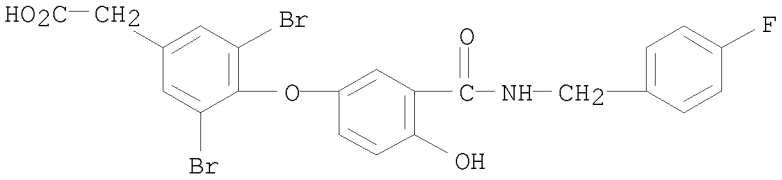

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:465510 CAPLUS
DOCUMENT NUMBER: 141:133551
TITLE: Thyroid receptor ligands. Part 2: thyromimetics with improved selectivity for the thyroid hormone receptor beta
AUTHOR(S): Hangeland, Jon J.; Doweyko, Arthur M.; Dejneka, Tamara; Friends, Todd J.; Devasthale, Pratik; Mellstrom, Karin; Sandberg, Johnny; Grynfarb, Marlena; Sack, John S.; Einspahr, Howard; Faernegardh, Mathias; Husman, Bolette; Ljunggren, Jan; Koehler, Konrad; Sheppard, Cheryl; Malm, Johan; Ryono, Denis E.
CORPORATE SOURCE: Pharmaceutical Research Institute, Bristol-Myers Squibb, Princeton, NJ, 08543, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2004), 14(13), 3549-3553
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:133551
AB A set of thyromimetics having improved selectivity for TR-β1 were prepared by replacing the 3'-iso-Pr group of 2 and 3 with substituents having increased steric bulk. From this limited SAR study, the most potent and selective compds. identified were derived from 2 and contained a 3'-Ph moiety bearing small hydrophobic groups meta to the biphenyl link. X-ray crystal data of 15c complexed with TR-β1 LBD shows methionine 442 to be displaced by the bulky R3' Ph Et amide side chain. Movement of this amino acid side chain provides an expanded pocket for the bulky side chain while the ligand-receptor complex retains full agonist activity.
IT 725239-20-3P 725239-64-5P 725239-65-6P
725239-66-7P 725239-67-8P 725239-69-0P
725239-70-3P 725239-71-4P 725239-72-5P
725239-73-6P 725239-74-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(structure activity relationships of thyromimetics with selectivity for thyroid hormone receptor beta)
RN 725239-20-3 CAPLUS
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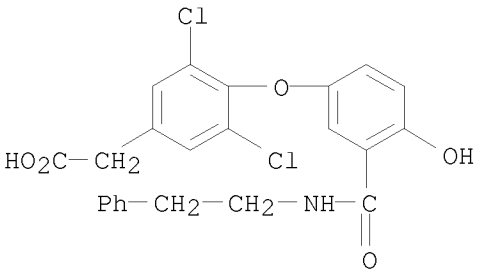

RN 725239-64-5 CAPLUS
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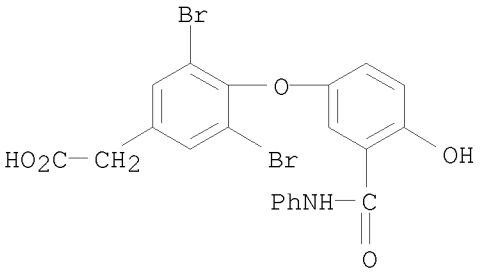

RN 725239-65-6 CAPLUS
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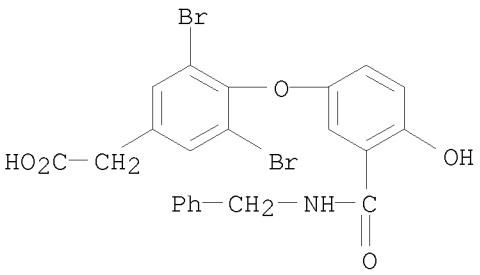
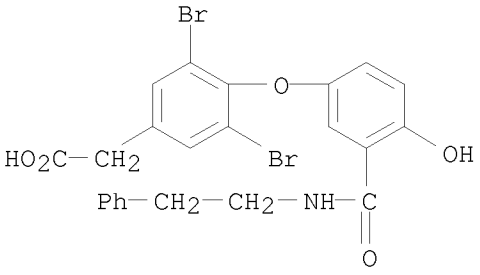
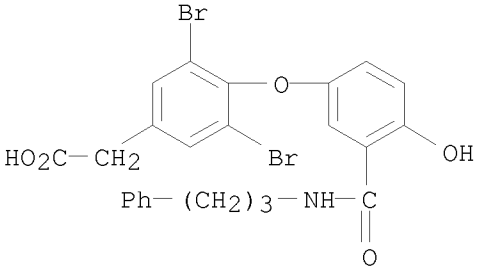


RN 725239-66-7 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[(2-phenylethyl)amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 725239-67-8 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[(3-phenylpropyl)amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 725239-69-0 CAPLUS
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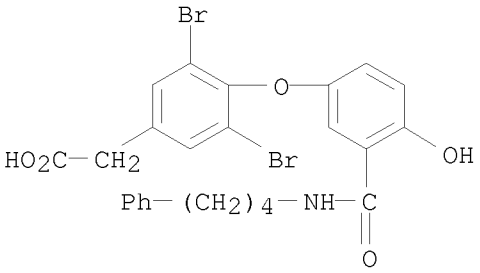
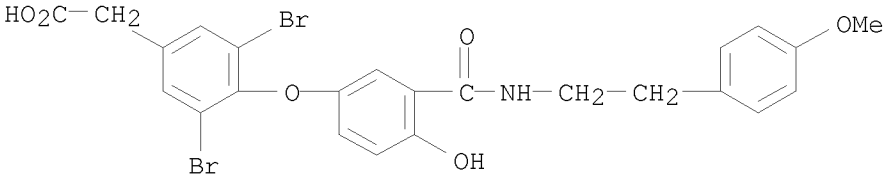
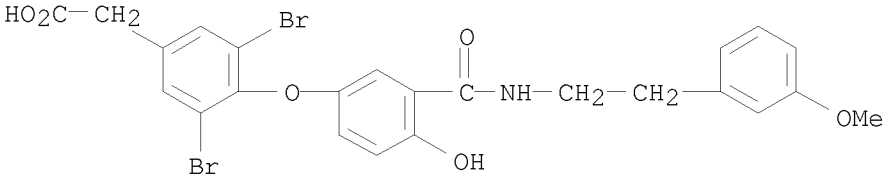


RN 725239-70-3 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[2-(4-methoxyphenyl)ethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 725239-71-4 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[2-(3-methoxyphenyl)ethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 725239-72-5 CAPLUS
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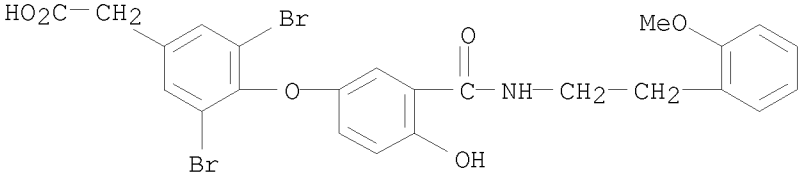

RN 725239-73-6 CAPLUS
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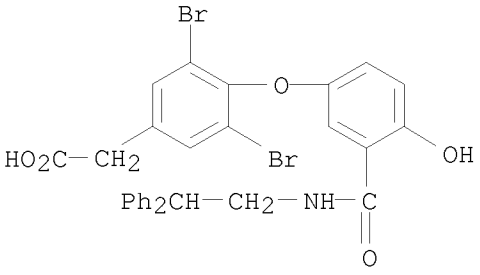

RN 725239-74-7 CAPLUS
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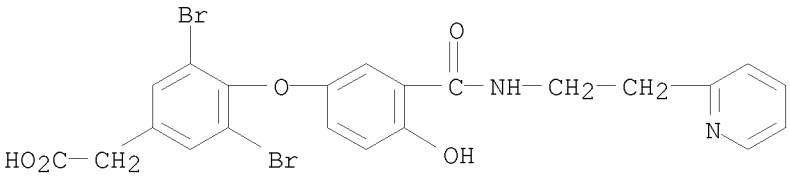

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> file caplus

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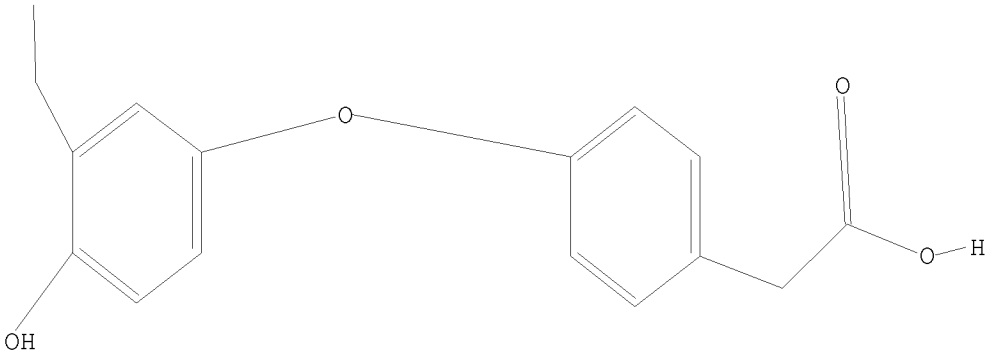

Structure attributes must be viewed using STN Express query preparation.

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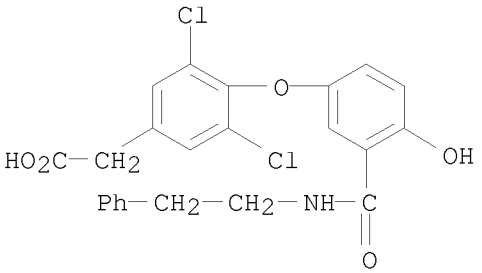
L7 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:632256 CAPLUS
DOCUMENT NUMBER: 147:226220
TITLE: QSAR study of selective ligands for the thyroid hormone receptor β
AUTHOR(S): Liu, Huanxiang; Gramatica, Paola
CORPORATE SOURCE: QSAR Research Unit in Environmental Chemistry and Ecotoxicology, Department of Structural and Functional

Biology, University of Insubria, Varese, 21100, Italy
SOURCE: Bioorganic & Medicinal Chemistry (2007), 15(15), 5251-5261
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this paper, an accurate and reliable QSAR model of 87 selective ligands for the thyroid hormone receptor β 1 (TRβ1) was developed, based on theor. mol. descriptors to predict the binding affinity of compds. with receptor. The structural characteristics of compds. were described wholly by a large amount of mol. structural descriptors calculated by DRAGON. Six most relevant structural descriptors to the studied activity were selected as the inputs of QSAR model by a robust optimization algorithm Genetic Algorithm. The built model was fully assessed by various validation methods, including internal and external validation, Y-randomization test, chemical applicability domain, and all the validations indicate that the QSAR model we proposed is robust and satisfactory. Thus, the built QSAR model can be used to fast and accurately predict the binding affinity of compds. (in the defined applicability domain) to TRβ1. At the same time, the model proposed could also identify and provide some insight into what structural features are related to the biol. activity of these compds. and provide some instruction for further designing the new selective ligands for TRβ1 with high activity.

IT 725239-20-3 725239-64-5 725239-65-6
725239-66-7 725239-67-8 725239-69-0
725239-70-3 725239-71-4 725239-72-5
725239-73-6 725239-74-7
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(QSAR of selective ligands for thyroid hormone receptor β)

RN 725239-20-3 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[4-hydroxy-3-[[(2-phenylethyl)amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 725239-64-5 CAPLUS
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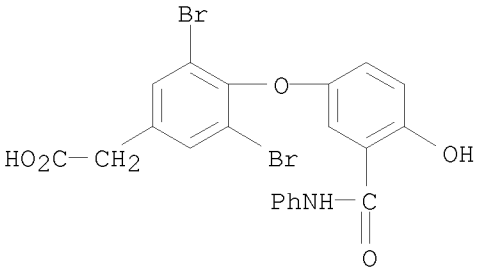

RN 725239-65-6 CAPLUS
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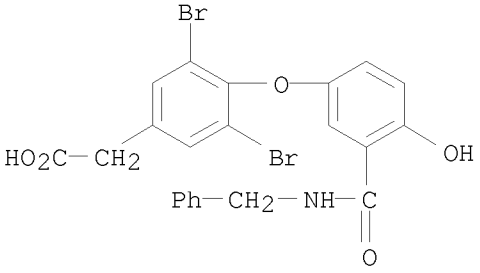
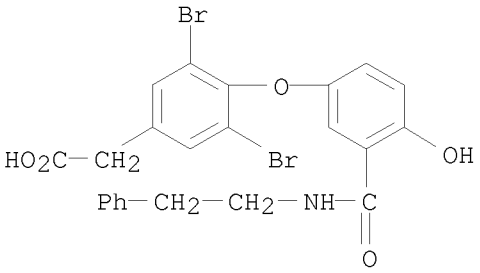
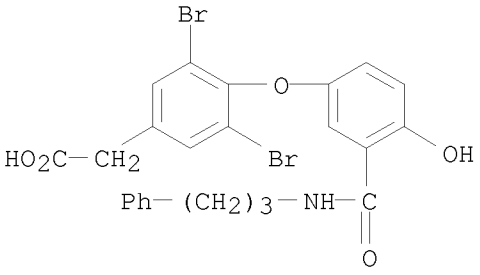


RN 725239-66-7 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[(2-phenylethyl)amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 725239-67-8 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[(3-phenylpropyl)amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 725239-69-0 CAPLUS
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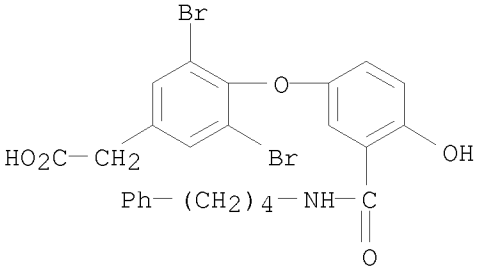
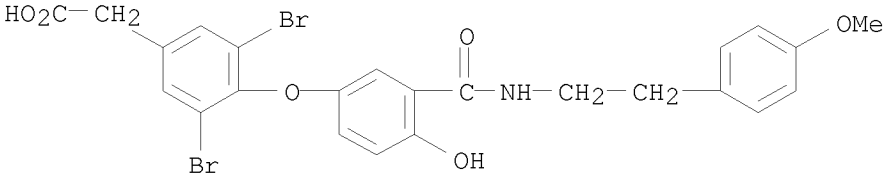


RN 725239-70-3 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[2-(4-methoxyphenyl)ethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 725239-71-4 CAPLUS
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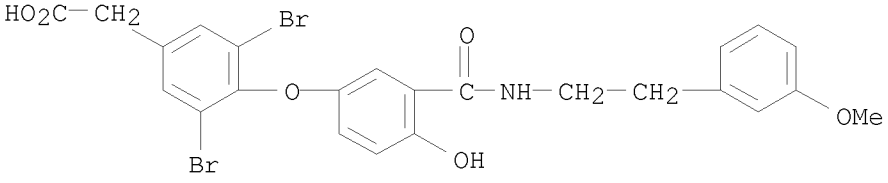
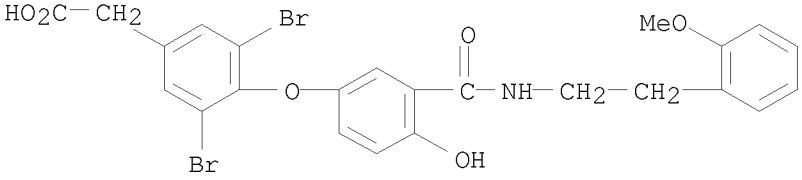
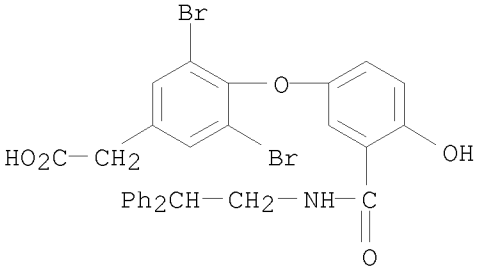


RN 725239-72-5 CAPLUS

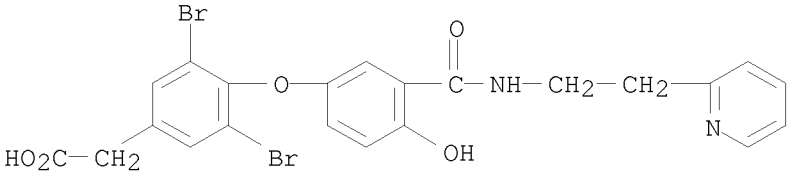
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[2-(2-methoxyphenyl)ethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 725239-73-6 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[3-[[(2,2-diphenylethyl)amino]carbonyl]-4-hydroxyphenoxy]- (CA INDEX NAME)



RN 725239-74-7 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[2-(2-pyridinyl)ethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

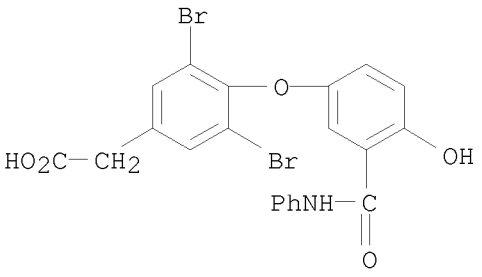
L7 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:590026 CAPLUS
DOCUMENT NUMBER: 147:226206
TITLE: 2D QSAR studies on thyroid hormone receptor ligands
AUTHOR(S): Valadares, Napoleao F.; Castilho, Marcelo S.; Polikarpov, Igor; Garratt, Richard C.
CORPORATE SOURCE: Departamento de Fisica e Informatica, Instituto de Fisica de Sao Carlos, Universidade de Sao Paulo, Sao Carlos-SP, 13560-970, Brazil
SOURCE: Bioorganic & Medicinal Chemistry (2007), 15(13), 4609-4617

CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 2D QSAR studies were carried out for a series of 55 ligands for the Thyroid receptors, TRα and TRβ. Significant cross-validated correlation coeffs. (q 2 = 0.781 (TRα) and 0.693 (TRβ)) were obtained. The models' predictive abilities were proved more valuable than the classical 2D-QSAR, and were further investigated by an external test set of 13 compds. The predicted values are in good agreement with exptl. values, suggesting that the models could be useful in the design of novel, more potent TR ligands. Contribution map anal. identified a number of positions that are promising for the development of receptor isoform specific ligands.

IT 725239-64-5
RL: PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
(QSAR studies on thyroid hormone receptor ligands)

RN 725239-64-5 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[(phenylamino)carbonyl]phenoxy]- (CA INDEX NAME)

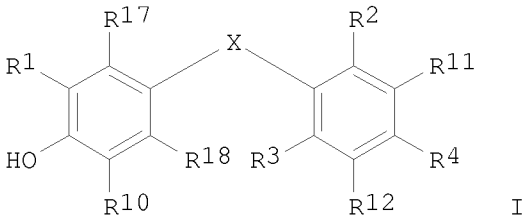


REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

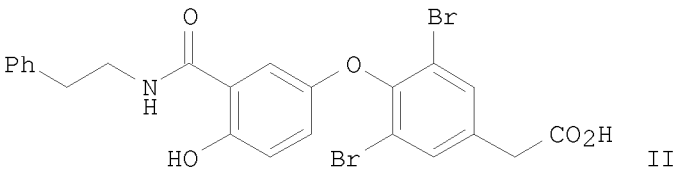
L7 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:927006 CAPLUS
DOCUMENT NUMBER: 141:395288
TITLE: New [3,5-dihalo-4-(4-hydroxyphenoxy)phenyl]acetic acid derivatives useful as thyroid receptor ligands, and their preparation, pharmaceutical compositions, and methods of use
INVENTOR(S): Ryono, Dennis E.; Hangeland, Jon J.; Friends, Todd J.; Dejneka, Tamara; Devasthale, Pratik; Caringal, Yolanda V.; Zhang, Minsheng; Doweyko, Arthur M. P.; Malm, Johan; Sanin, Andrei
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004093799	A2	20041104	WO 2004-US11883	20040416
WO 2004093799	A3	20050224		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
US 20050004184	A1	20050106	US 2004-826100	20040415
PRIORITY APPLN. INFO.:			US 2003-463774P P	20030418
OTHER SOURCE(S):	MARPAT 141:395288			

GI



I



II

AB Thyroid receptor ligands are provided which have the general formula I [wherein: R1 = (un)substituted CONR5R6, CH2NR5R6, NR5COR6, OR7, R8, 4-R9-4,5-dihydrooxazol-2-yl; R2, R3 = H, halo, C1-4 alkyl or C3-5 cycloalkyl, provided that at least 1 of R2 and R3 ≠ H; R4 = (CH2)nR13 or (CH2)nCONR16CR13R14R15; R5, R6 = H, (hetero)aryl, (cyclo)alkyl, or (hetero)aralkyl; R7 = (hetero)aryl, alkyl, or (hetero)aralkyl; R8 = (hetero)aryl or cycloalkyl; R9 = R7 or H; R10 = H, halo, cyano, or alkyl; R11, R12 = H, halo, alkoxy, OH, cyano, or alkyl; R13 = COOH and esters, phosphonic and phosphinic acid and esters, sulfonic acid, tetrazole, hydroxamic acid, thiazolidinedione, acylsulfonamide, or other carboxylic acid surrogates; R14, R15 = H, alkyl; or R14R15 = (CH2)2-5, forming 3- to 6-membered cycloalkyl rings; R16 = H or C1-4

alkyl; R17 and R18 = H, halo, or alkyl; n = 0-4; X = O, S, S(O)2, S(O), Se, CO, NH, or CH2]. In addition, a method is provided for preventing, inhibiting or treating diseases or disorders associated with metabolism dysfunction, or which are dependent upon the expression of, a T3 regulated gene, wherein a compound I is administered therapeutically. Claims cover the above, as well as pharmaceutical compns. containing I, and methods of coadministration of I with other compds., particularly certain antidiabetic agents. Compds. I include selective agonists, partial agonists, antagonists, and partial antagonists of thyroid receptors (no data). Approx. 168 compds. were prepared For instance, Me (3,5-dibromo-4-hydroxyphenyl)acetate underwent O-arylation with (4-MeOC6H4)2I+ BF4-, and the resultant 4-methoxyphenyl ether derivative underwent a sequence of: (1) formylation in the 3-position, (2) O-demethylation, (3) oxidation of the aldehyde to an acid, (4) amidation of the acid, and (5) alkaline saponification of the ester, to give title compound II.

IT 725239-20-3P 725239-64-5P 725239-65-6P
725239-66-7P 725239-67-8P 725239-69-0P
725239-70-3P 725239-71-4P 725239-72-5P
725239-73-6P 788822-75-3P 788822-76-4P
788822-77-5P 788822-78-6P 788822-79-7P
788822-80-0P 788822-81-1P 788822-82-2P
788822-83-3P 788822-84-4P 788822-85-5P
788822-86-6P 788822-87-7P 788822-88-8P
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788822-92-4P 788822-93-5P 788822-94-6P
788822-95-7P 788822-96-8P 788822-97-9P
788822-98-0P 788822-99-1P 788823-00-7P
788823-01-8P 788823-02-9P 788823-03-0P
788823-04-1P 788823-05-2P 788823-06-3P
788823-07-4P 788823-08-5P 788823-09-6P
788823-10-9P 788823-11-0P 788823-12-1P
788823-13-2P 788823-15-4P 788823-16-5P
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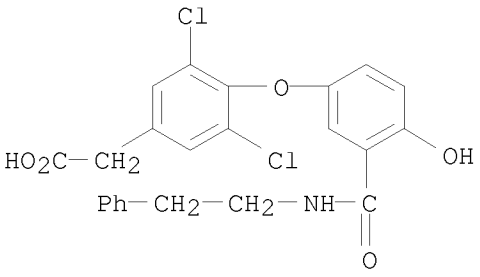
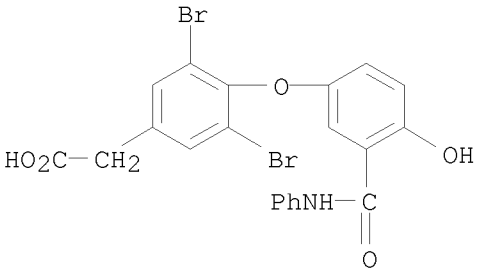
788823-20-1P 788823-21-2P 788823-22-3P
788823-23-4P 788823-24-5P 788823-25-6P
788823-26-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of [dihalo(hydroxyphenoxy)phenyl]acetic acid derivs. as thyroid receptor ligands)

RN 725239-20-3 CAPLUS

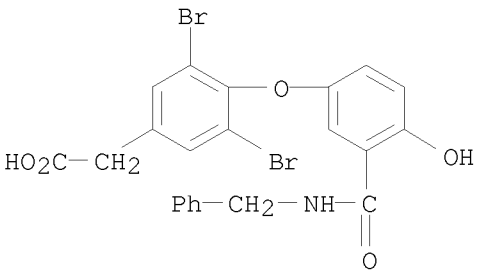
CN Benzeneacetic acid, 3,5-dichloro-4-[4-hydroxy-3-[[(2-phenylethyl)amino]carbonyl]phenoxy]- (CA INDEX NAME)



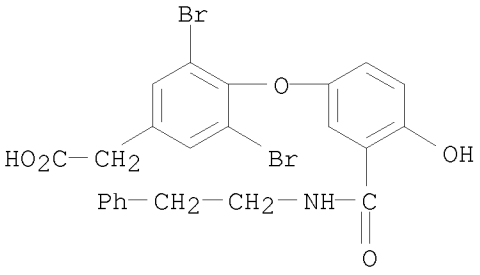
RN 725239-64-5 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[(phenylamino)carbonyl]phenoxy]- (CA INDEX NAME)



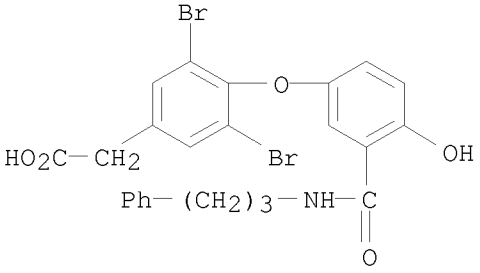
RN 725239-65-6 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[(phenylmethyl)amino]carbonyl]phenoxy]- (CA INDEX NAME)



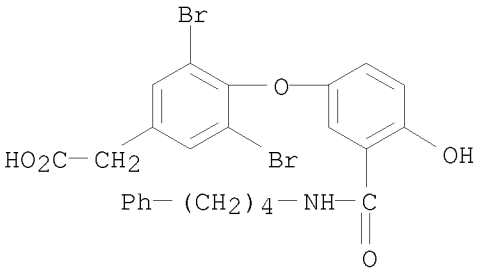
RN 725239-66-7 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[(2-phenylethyl)amino]carbonyl]phenoxy]- (CA INDEX NAME)



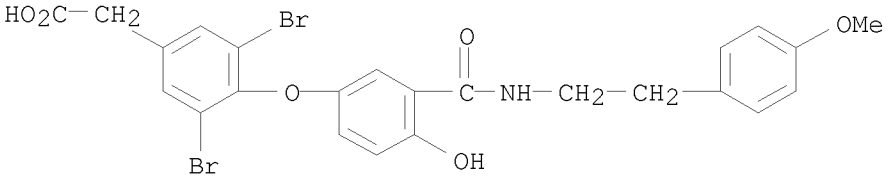
RN 725239-67-8 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[(3-phenylpropyl)amino]carbonyl]phenoxy]- (CA INDEX NAME)



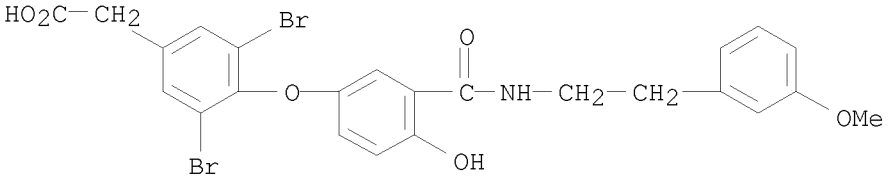
RN 725239-69-0 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[(4-phenylbutyl)amino]carbonyl]phenoxy]- (CA INDEX NAME)



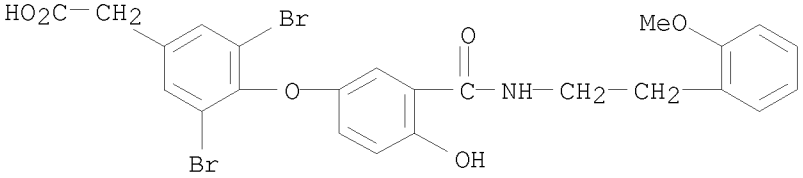
RN 725239-70-3 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[2-(4-methoxyphenyl)ethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



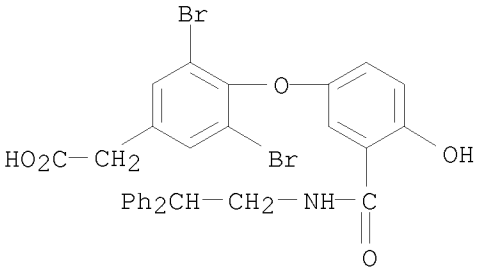
RN 725239-71-4 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[2-(3-methoxyphenyl)ethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



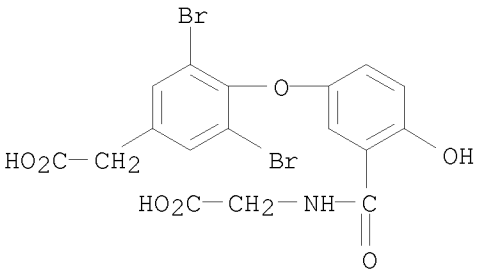
RN 725239-72-5 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[2-(2-methoxyphenyl)ethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 725239-73-6 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[3-[[(2,2-diphenylethyl)amino]carbonyl]-4-hydroxyphenoxy]- (CA INDEX NAME)

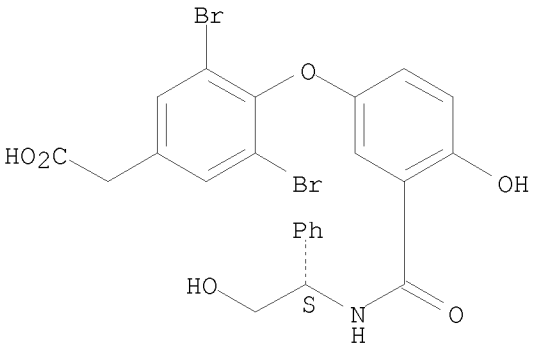


RN 788822-75-3 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[3-[[(carboxymethyl)amino]carbonyl]-4-hydroxyphenoxy]- (CA INDEX NAME)



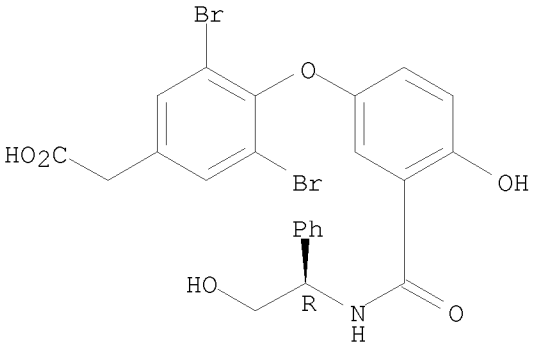
RN 788822-76-4 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1S)-2-hydroxy-1-phenylethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.



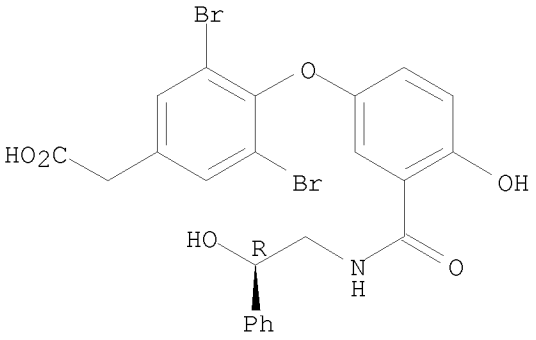
RN 788822-77-5 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1R)-2-hydroxy-1-phenylethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.



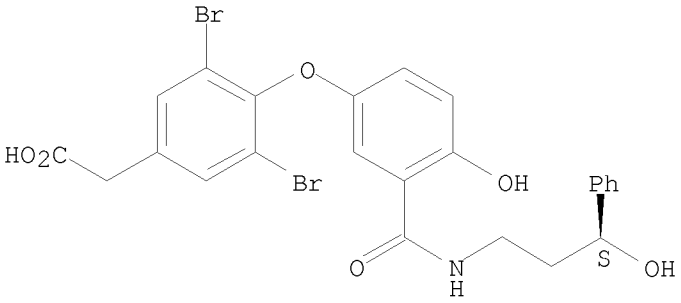
RN 788822-78-6 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(2R)-2-hydroxy-2-phenylethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.



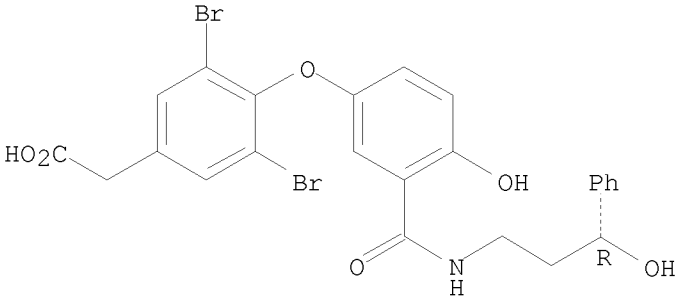
RN 788822-79-7 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(3S)-3-hydroxy-3-phenylpropyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.



RN 788822-80-0 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(3R)-3-hydroxy-3-phenylpropyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

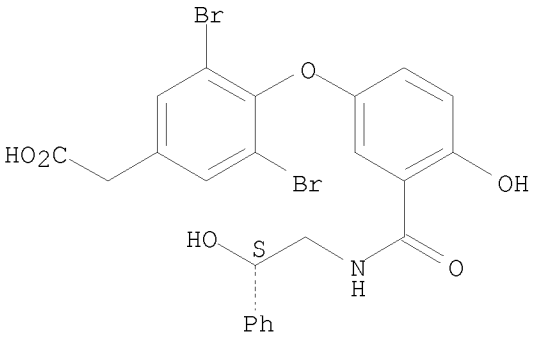
Absolute stereochemistry.



RN 788822-81-1 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(2S)-2-hydroxy-2-

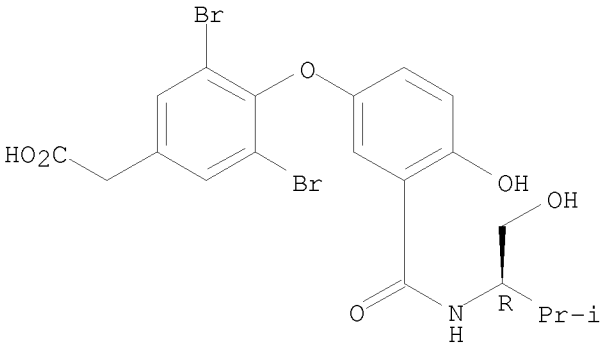
phenylethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.



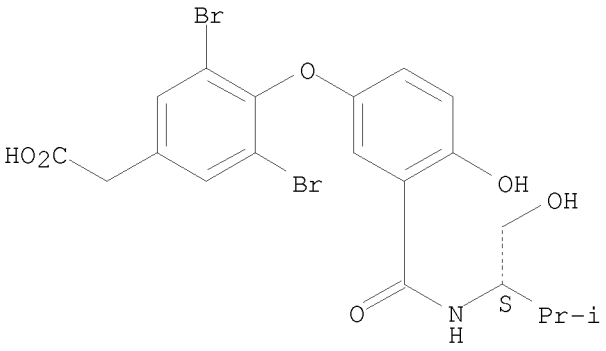
RN 788822-82-2 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1R)-1-(hydroxymethyl)-2-methylpropyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.



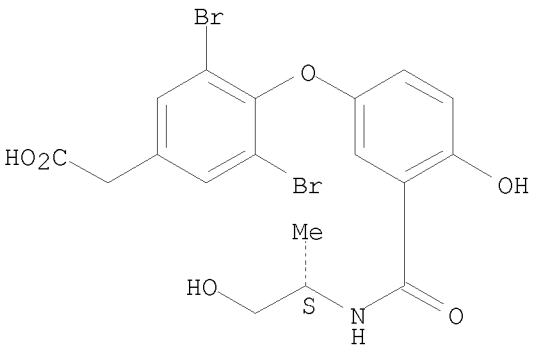
RN 788822-83-3 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1S)-1-(hydroxymethyl)-2-methylpropyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.



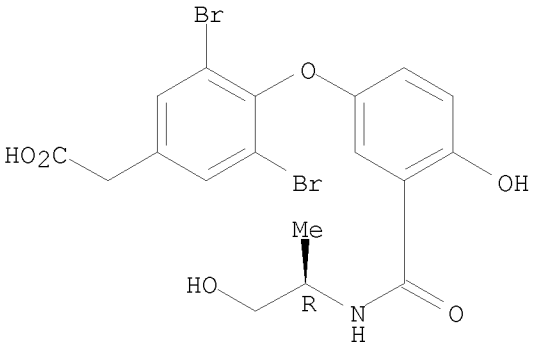
RN 788822-84-4 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1S)-2-hydroxy-1-methylethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.

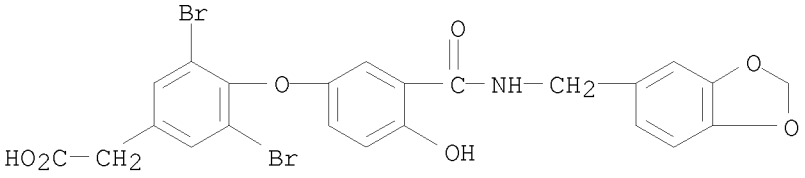


RN 788822-85-5 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1R)-2-hydroxy-1-methylethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

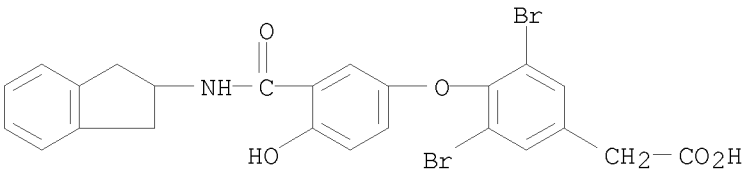
Absolute stereochemistry.



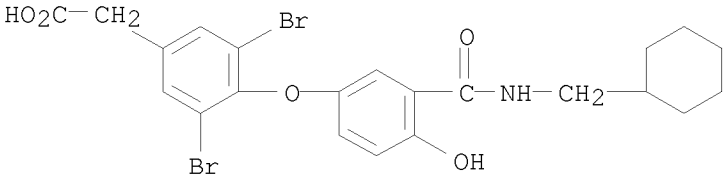
RN 788822-86-6 CAPLUS
CN Benzeneacetic acid, 4-[3-[[(1,3-benzodioxol-5-ylmethyl)amino]carbonyl]-4-hydroxyphenoxy]-3,5-dibromo- (CA INDEX NAME)



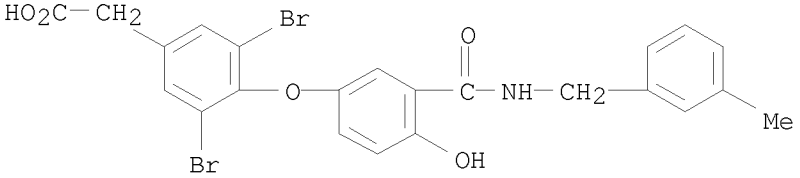
RN 788822-87-7 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[3-[[(2,3-dihydro-1H-inden-2-yl)amino]carbonyl]-4-hydroxyphenoxy]- (CA INDEX NAME)



RN 788822-88-8 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[3-[[(cyclohexylmethyl)amino]carbonyl]-4-hydroxyphenoxy]- (CA INDEX NAME)

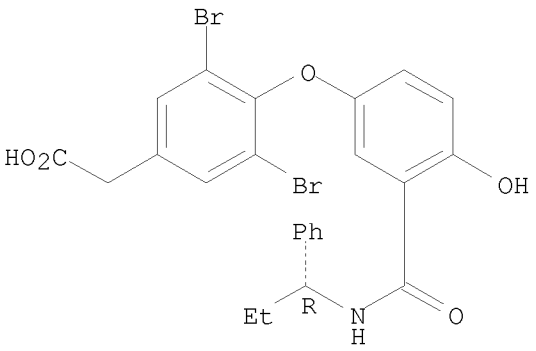


RN 788822-89-9 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(3-methylphenyl)methyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



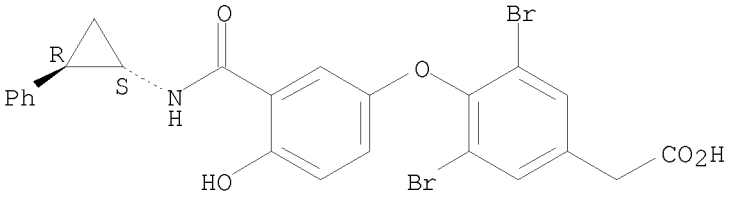
RN 788822-90-2 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1R)-1-phenylpropyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

Absolute stereochemistry.



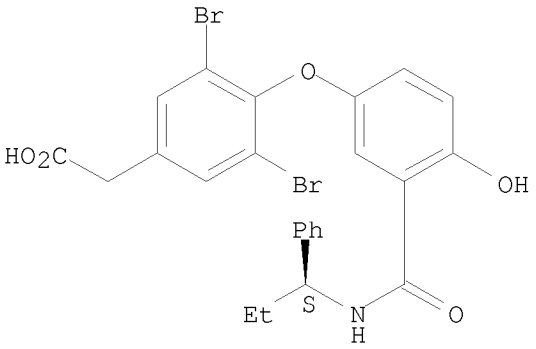
RN 788822-91-3 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1R,2S)-2-phenylcyclopropyl]amino]carbonyl]phenoxy]-, rel- (CA INDEX NAME)

Relative stereochemistry.

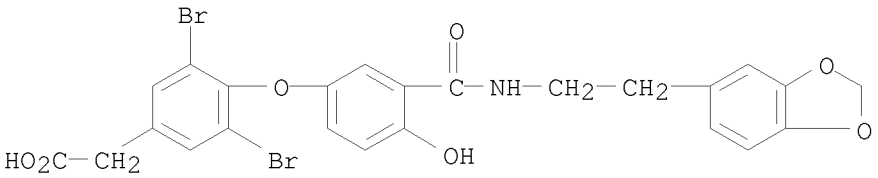


RN 788822-92-4 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1S)-1-phenylpropyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

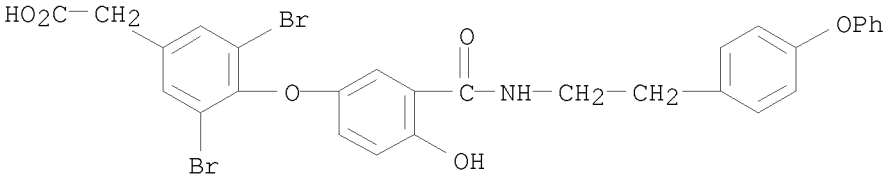
Absolute stereochemistry.



RN 788822-93-5 CAPLUS
CN Benzeneacetic acid, 4-[3-[[[2-(1,3-benzodioxol-5-yl)ethyl]amino]carbonyl]-4-hydroxyphenoxy]-3,5-dibromo- (CA INDEX NAME)

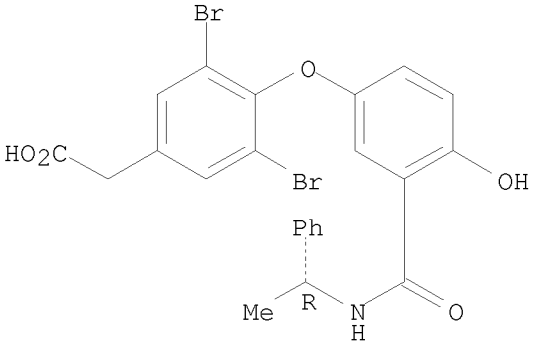


RN 788822-94-6 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[2-(4-phenoxyphenyl)ethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

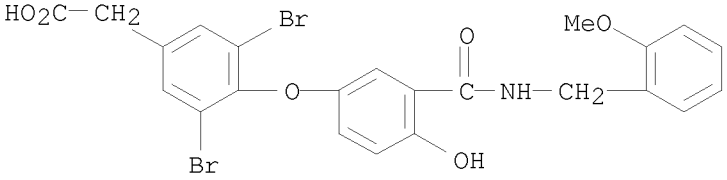


RN 788822-95-7 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1R)-1-phenylethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

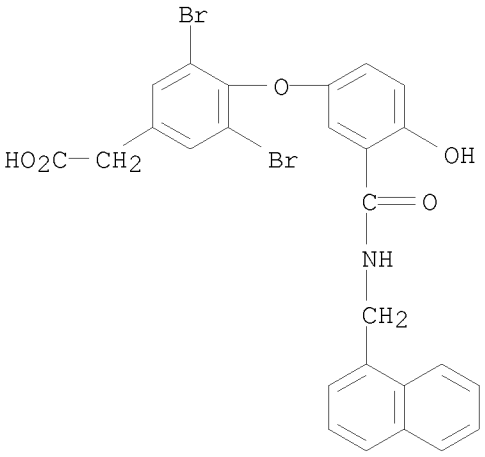
Absolute stereochemistry.



RN 788822-96-8 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(2-methoxyphenyl)methyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

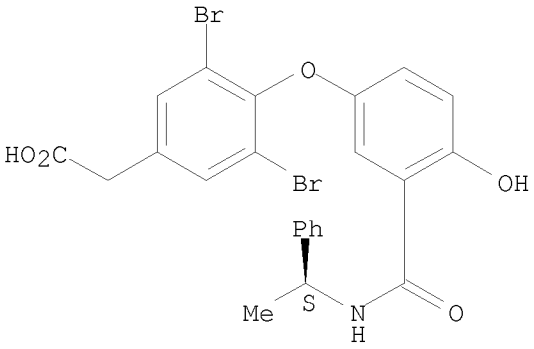


RN 788822-97-9 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[(1-naphthalenylmethyl)amino]carbonyl]phenoxy]- (CA INDEX NAME)

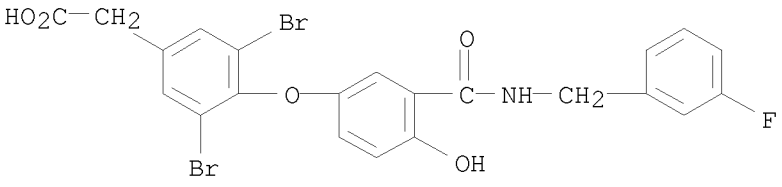


RN 788822-98-0 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(1S)-1-phenylethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)

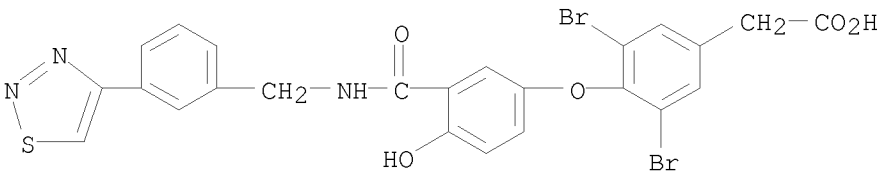
Absolute stereochemistry.



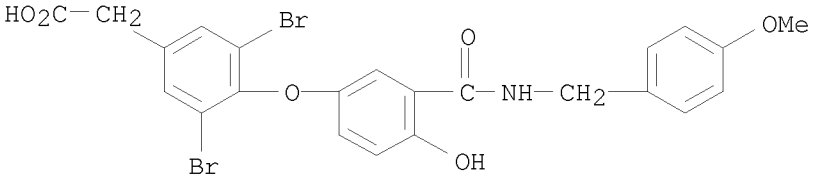
RN 788822-99-1 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[3-[[[(3-fluorophenyl)methyl]amino]carbonyl]-4-hydroxyphenoxy]- (CA INDEX NAME)



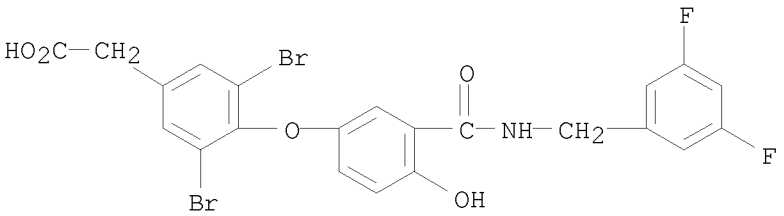
RN 788823-00-7 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[[3-(1,2,3-thiadiazol-4-yl)phenyl]methyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 788823-01-8 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[(4-methoxyphenyl)methyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 788823-02-9 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[3-[[[(3,5-difluorophenyl)methyl]amino]carbonyl]-4-hydroxyphenoxy]- (CA INDEX NAME)



RN 788823-03-0 CAPLUS
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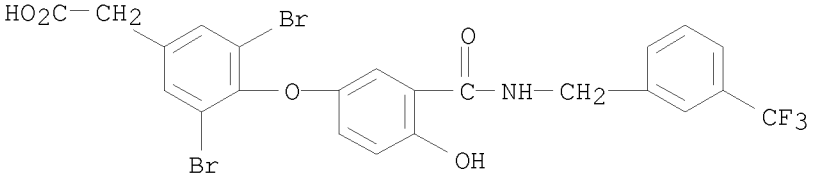

RN 788823-04-1 CAPLUS
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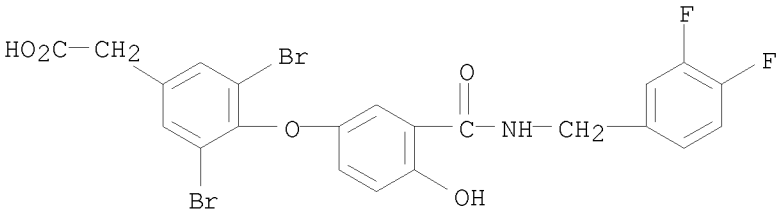
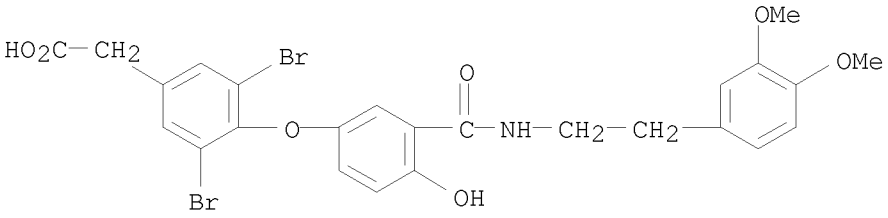


RN 788823-05-2 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[3-[[[2-(3,4-dimethoxyphenyl)ethyl]amino]carbonyl]-4-hydroxyphenoxy]- (CA INDEX NAME)



RN 788823-06-3 CAPLUS
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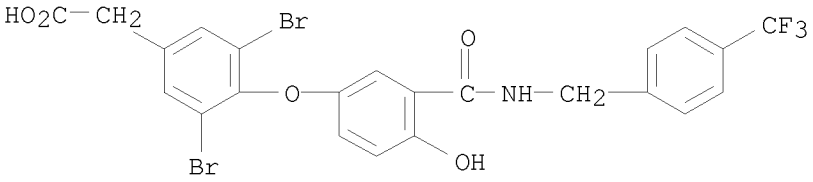
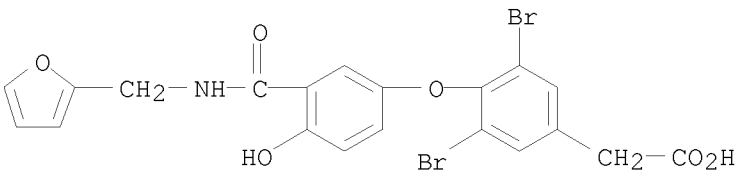


RN 788823-07-4 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[3-[[(2-furanylmethyl)amino]carbonyl]-4-hydroxyphenoxy]- (CA INDEX NAME)



RN 788823-08-5 CAPLUS
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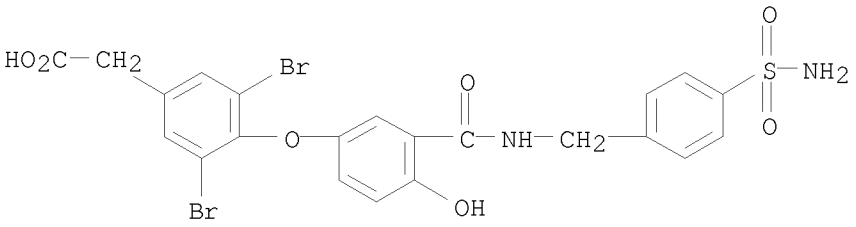
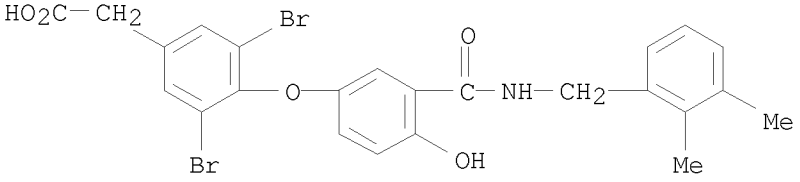
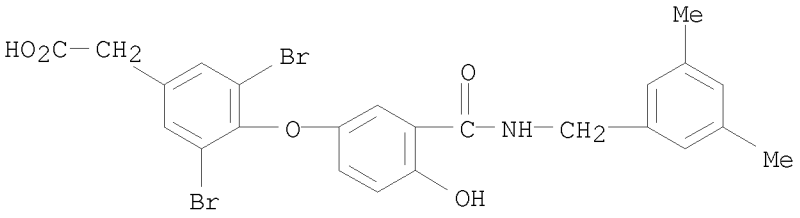


RN 788823-09-6 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[3-[[[(2,3-dimethylphenyl)methyl]amino]carbonyl]-4-hydroxyphenoxy]- (CA INDEX NAME)



RN 788823-10-9 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[3-[[[(3,5-dimethylphenyl)methyl]amino]carbonyl]-4-hydroxyphenoxy]- (CA INDEX NAME)



RN 788823-11-0 CAPLUS
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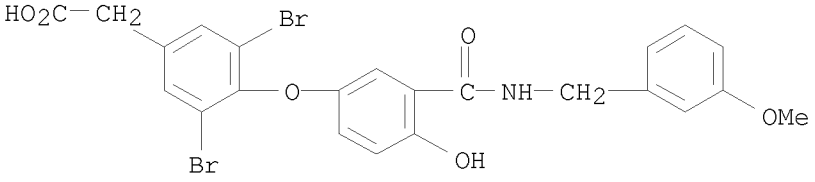

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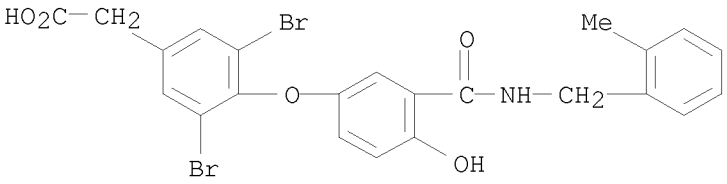
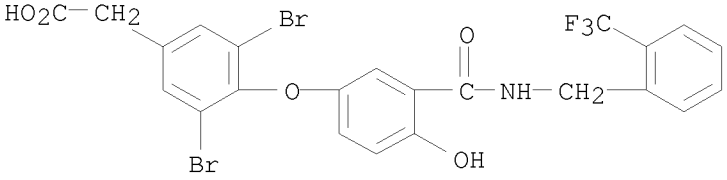


RN 788823-13-2 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[[2-(trifluoromethyl)phenyl]methyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 788823-15-4 CAPLUS
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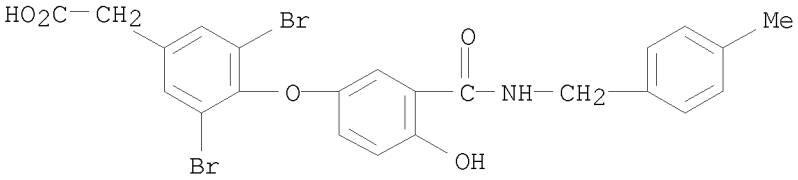

RN 788823-16-5 CAPLUS
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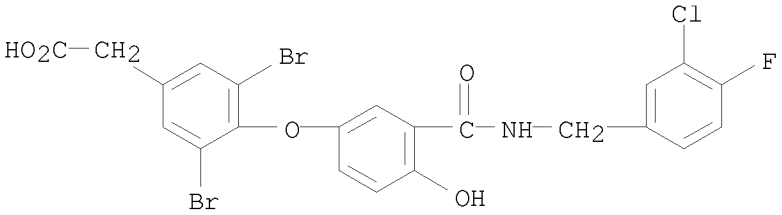

RN 788823-17-6 CAPLUS
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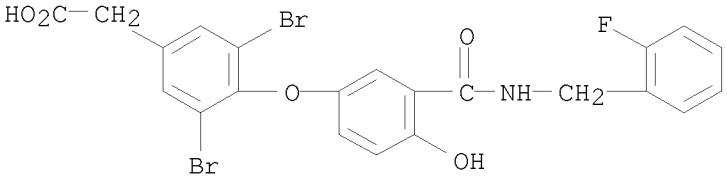

RN 788823-18-7 CAPLUS
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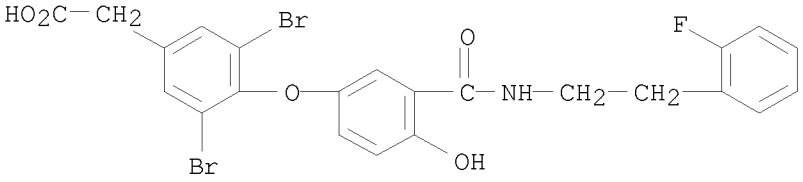

RN 788823-19-8 CAPLUS
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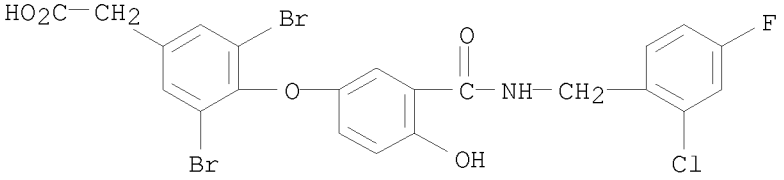

RN 788823-20-1 CAPLUS
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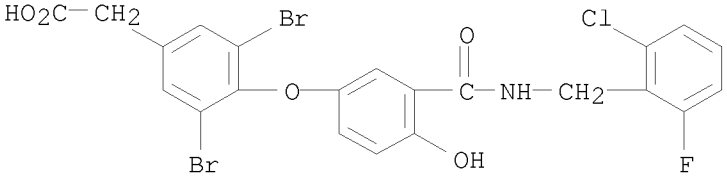

RN 788823-21-2 CAPLUS
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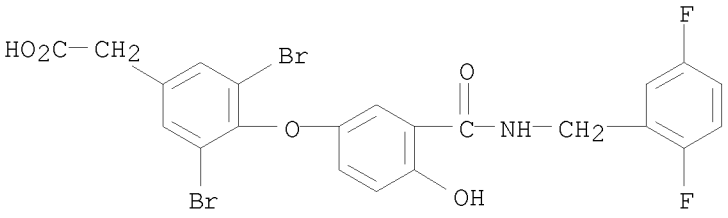

RN 788823-22-3 CAPLUS
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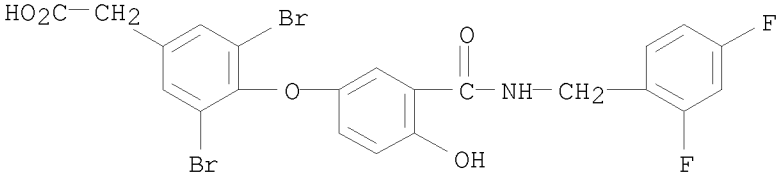

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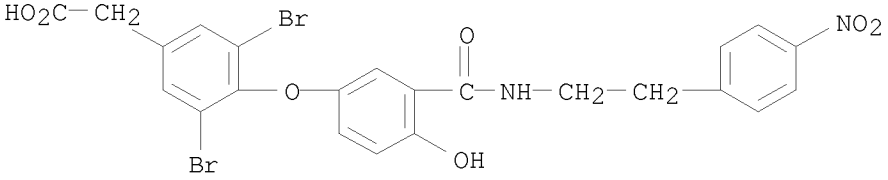

RN 788823-24-5 CAPLUS
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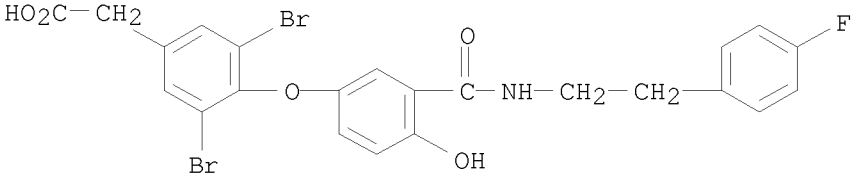

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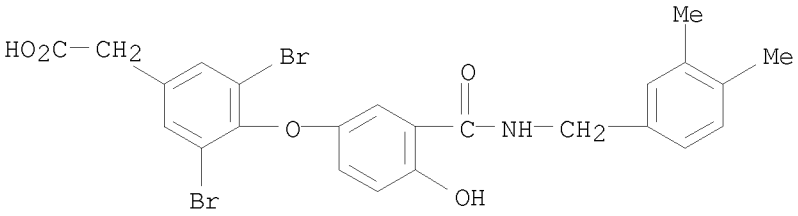

RN 788823-26-7 CAPLUS
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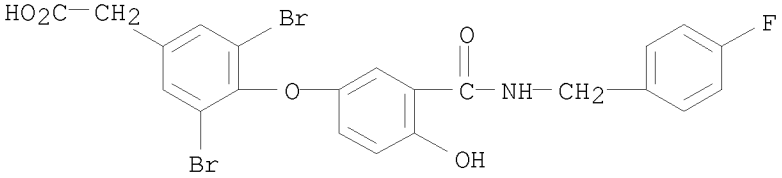
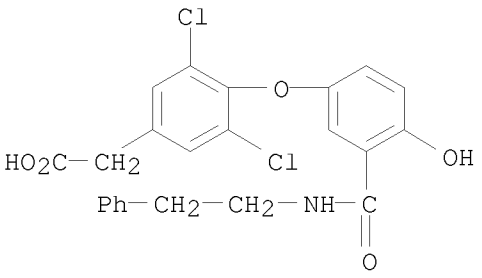


REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:465510 CAPLUS
DOCUMENT NUMBER: 141:133551
TITLE: Thyroid receptor ligands. Part 2: thyromimetics with improved selectivity for the thyroid hormone receptor beta
AUTHOR(S): Hangeland, Jon J.; Doweyko, Arthur M.; Dejneka, Tamara; Friends, Todd J.; Devasthale, Pratik; Mellstrom, Karin; Sandberg, Johnny; Grynfarb, Marlena; Sack, John S.; Einspahr, Howard; Faernegardh, Mathias; Husman, Bolette; Ljunggren, Jan; Koehler, Konrad; Sheppard, Cheryl; Malm, Johan; Ryono, Denis E.
CORPORATE SOURCE: Pharmaceutical Research Institute, Bristol-Myers Squibb, Princeton, NJ, 08543, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2004), 14(13), 3549-3553
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:133551
AB A set of thyromimetics having improved selectivity for TR-β1 were prepared by replacing the 3'-iso-Pr group of 2 and 3 with substituents having increased steric bulk. From this limited SAR study, the most potent and selective compds. identified were derived from 2 and contained a 3'-Ph moiety bearing small hydrophobic groups meta to the biphenyl link. X-ray crystal data of 15c complexed with TR-β1 LBD shows methionine 442 to be displaced by the bulky R3' Ph Et amide side chain. Movement of this amino acid side chain provides an expanded pocket for the bulky side chain while the ligand-receptor complex retains full agonist activity.

IT 725239-20-3P 725239-64-5P 725239-65-6P
725239-66-7P 725239-67-8P 725239-69-0P
725239-70-3P 725239-71-4P 725239-72-5P
725239-73-6P 725239-74-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(structure activity relationships of thyromimetics with selectivity for thyroid hormone receptor beta)

RN 725239-20-3 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[4-hydroxy-3-[[(2-phenylethyl)amino]carbonyl]phenoxy]- (CA INDEX NAME)



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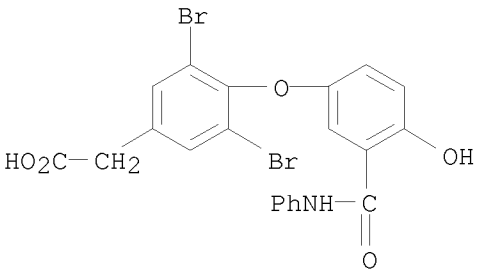

RN 725239-65-6 CAPLUS
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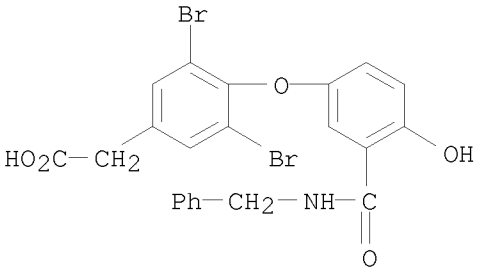
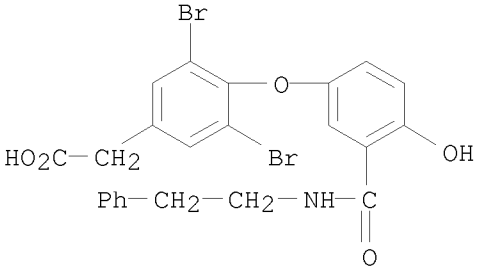
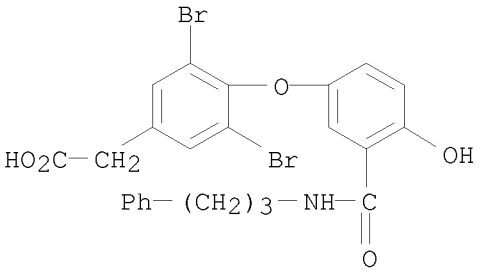


RN 725239-66-7 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[(2-phenylethyl)amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 725239-67-8 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[(3-phenylpropyl)amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 725239-69-0 CAPLUS
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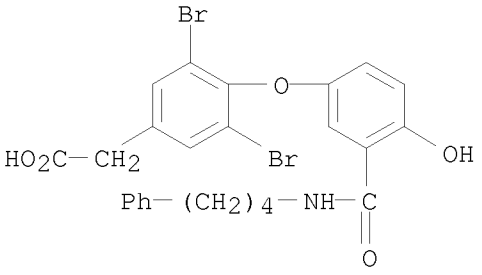
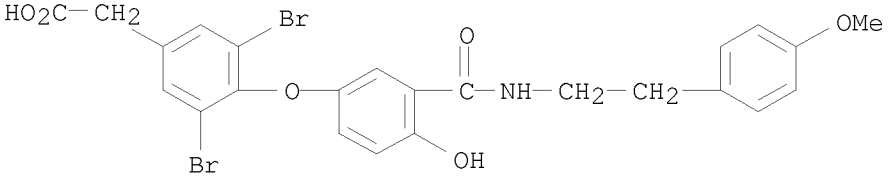
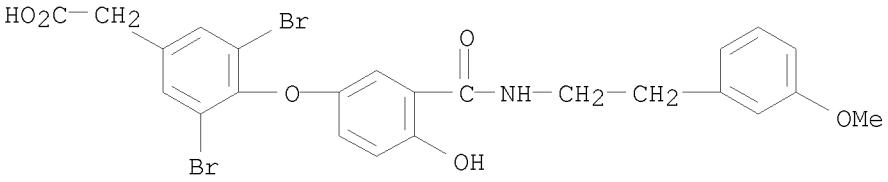


RN 725239-70-3 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[2-(4-methoxyphenyl)ethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 725239-71-4 CAPLUS
CN Benzeneacetic acid, 3,5-dibromo-4-[4-hydroxy-3-[[[2-(3-methoxyphenyl)ethyl]amino]carbonyl]phenoxy]- (CA INDEX NAME)



RN 725239-72-5 CAPLUS
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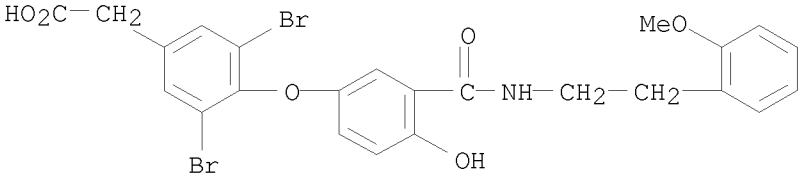

RN 725239-73-6 CAPLUS
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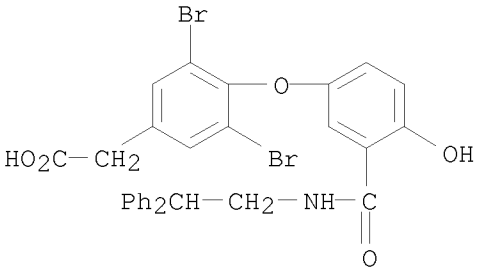

RN 725239-74-7 CAPLUS
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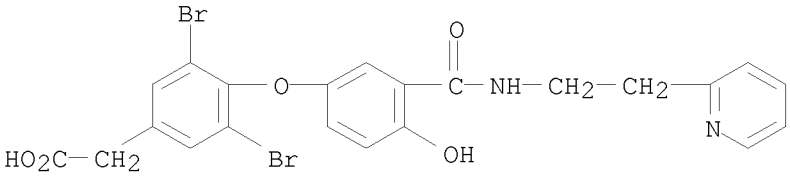

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L9 STRUCTURE UPLOADED

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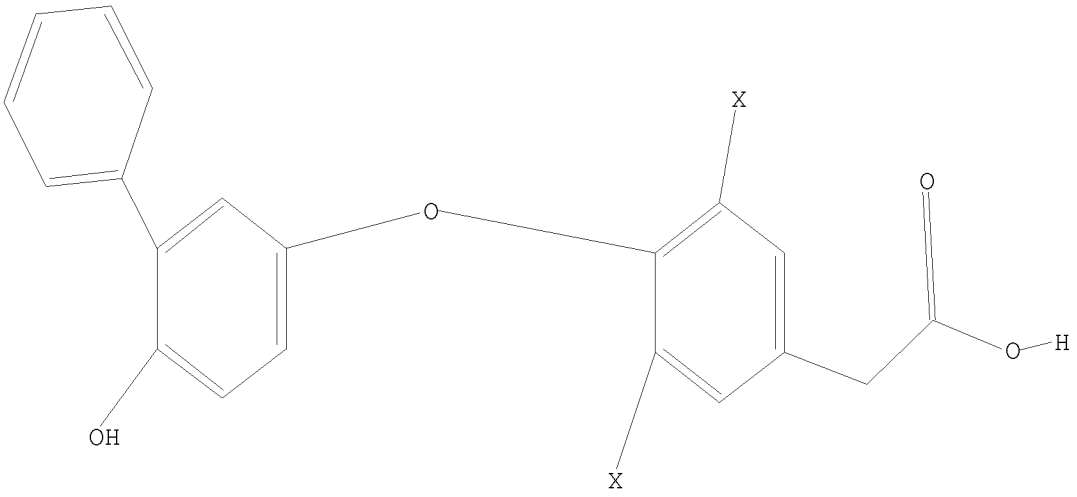
L9 HAS NO ANSWERS
L9 STR



Structure attributes must be viewed using STN Express query preparation.

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Substance data SEARCH and crossover from CAS REGISTRY in progress...
Use DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.

FULL SEARCH INITIATED 18:10:29 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 334 TO ITERATE

100.0% PROCESSED 334 ITERATIONS 38 ANSWERS
SEARCH TIME: 00.00.01

L10 38 SEA SSS FUL L9

L11 5 L10

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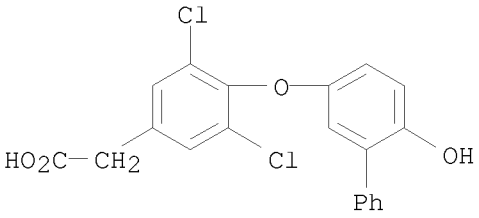
L11 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:632256 CAPLUS
DOCUMENT NUMBER: 147:226220
TITLE: QSAR study of selective ligands for the thyroid hormone receptor β
AUTHOR(S): Liu, Huanxiang; Gramatica, Paola
CORPORATE SOURCE: QSAR Research Unit in Environmental Chemistry and Ecotoxicology, Department of Structural and Functional Biology, University of Insubria, Varese, 21100, Italy
SOURCE: Bioorganic & Medicinal Chemistry (2007), 15(15), 5251-5261
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In this paper, an accurate and reliable QSAR model of 87 selective ligands for the thyroid hormone receptor β 1 (TRβ1) was developed, based on theor. mol. descriptors to predict the binding affinity of compds. with receptor. The structural characteristics of compds. were described wholly by a large amount of mol. structural descriptors calculated by DRAGON. Six most relevant structural descriptors to the studied activity were selected as the inputs of QSAR model by a robust optimization algorithm Genetic Algorithm. The built model was fully assessed by various validation methods, including internal and external validation, Y-randomization test,

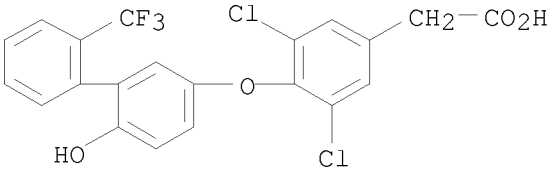
chemical applicability domain, and all the validations indicate that the QSAR model we proposed is robust and satisfactory. Thus, the built QSAR model can be used to fast and accurately predict the binding affinity of compds. (in the defined applicability domain) to TRβ1. At the same time, the model proposed could also identify and provide some insight into what structural features are related to the biol. activity of these compds. and provide some instruction for further designing the new selective ligands for TRβ1 with high activity.

IT 725239-22-5 725239-24-7 725239-26-9
725239-28-1 725239-30-5 725239-32-7
725239-34-9 725239-35-0 725239-37-2
725239-39-4 725239-41-8 725239-43-0
725239-45-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(QSAR of selective ligands for thyroid hormone receptor β)

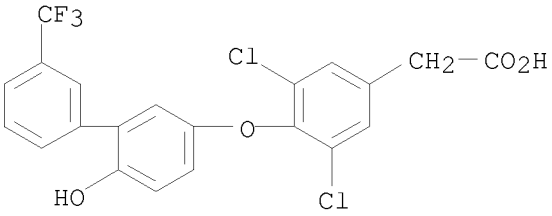
RN 725239-22-5 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(6-hydroxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



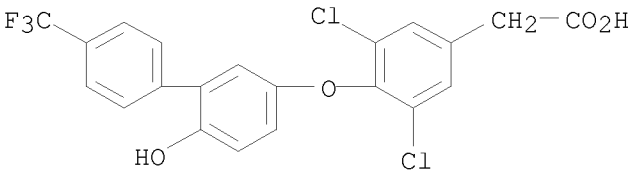
RN 725239-24-7 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[[6-hydroxy-2'-(trifluoromethyl)[1,1'-biphenyl]-3-yl]oxy]- (CA INDEX NAME)



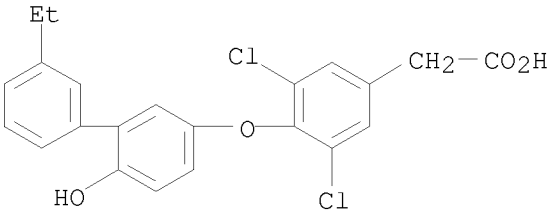
RN 725239-26-9 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[[6-hydroxy-3'-(trifluoromethyl)[1,1'-biphenyl]-3-yl]oxy]- (CA INDEX NAME)



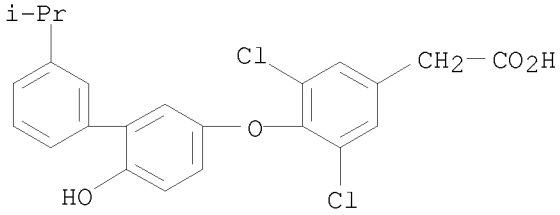
RN 725239-28-1 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[[6-hydroxy-4'-(trifluoromethyl)[1,1'-biphenyl]-3-yl]oxy]- (CA INDEX NAME)



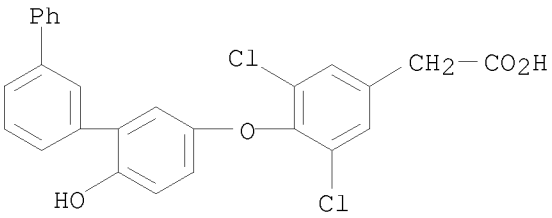
RN 725239-30-5 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(3'-ethyl-6-hydroxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



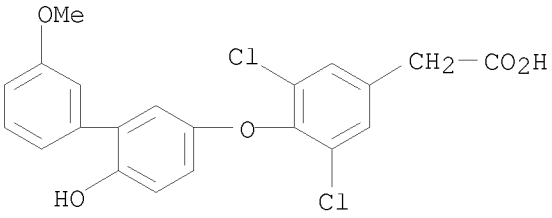
RN 725239-32-7 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[[6-hydroxy-3'-(1-methylethyl)[1,1'-biphenyl]-3-yl]oxy]- (CA INDEX NAME)



RN 725239-34-9 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(6-hydroxy[1,1':3',1''-terphenyl]-3-yl)oxy]- (CA INDEX NAME)



RN 725239-35-0 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(6-hydroxy-3'-methoxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



RN 725239-37-2 CAPLUS
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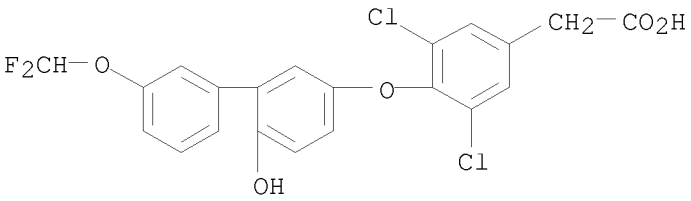
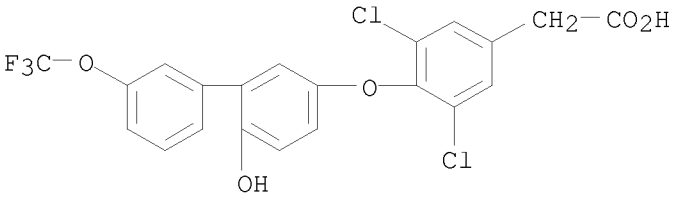
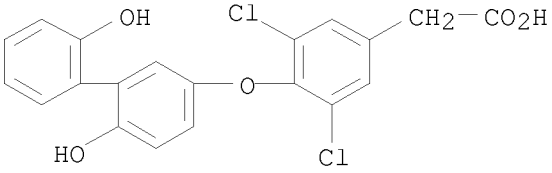


RN 725239-39-4 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[[6-hydroxy-3'-(trifluoromethoxy)[1,1'-biphenyl]-3-yl]oxy]- (CA INDEX NAME)

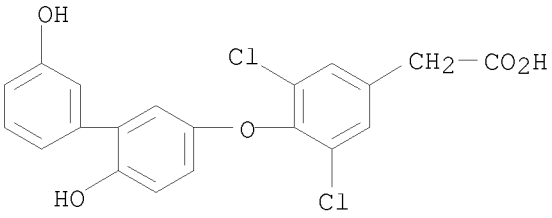


RN 725239-41-8 CAPLUS

CN Benzeneacetic acid, 3,5-dichloro-4-[(2',6-dihydroxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



RN 725239-43-0 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(3',6-dihydroxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



RN 725239-45-2 CAPLUS
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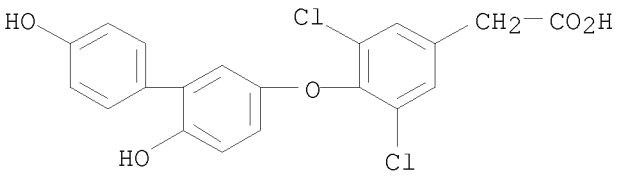


REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

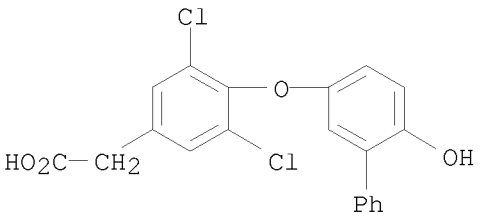
L11 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:590026 CAPLUS
DOCUMENT NUMBER: 147:226206
TITLE: 2D QSAR studies on thyroid hormone receptor ligands
AUTHOR(S): Valadares, Napoleao F.; Castilho, Marcelo S.; Polikarpov, Igor; Garratt, Richard C.
CORPORATE SOURCE: Departamento de Fisica e Informatica, Instituto de Fisica de Sao Carlos, Universidade de Sao Paulo, Sao Carlos-SP, 13560-970, Brazil
SOURCE: Bioorganic & Medicinal Chemistry (2007), 15(13), 4609-4617
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.

DOCUMENT TYPE: Journal
LANGUAGE: English

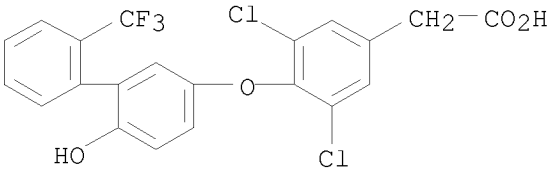
AB 2D QSAR studies were carried out for a series of 55 ligands for the Thyroid receptors, TRα and TRβ. Significant cross-validated correlation coeffs. (q 2 = 0.781 (TRα) and 0.693 (TRβ)) were obtained. The models' predictive abilities were proved more valuable than the classical 2D-QSAR, and were further investigated by an external test set of 13 compds. The predicted values are in good agreement with exptl. values, suggesting that the models could be useful in the design of novel, more potent TR ligands. Contribution map anal. identified a number of positions that are promising for the development of receptor isoform specific ligands.

IT 725239-22-5 725239-24-7 725239-34-9
725239-39-4 725239-43-0
RL: PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
(QSAR studies on thyroid hormone receptor ligands)

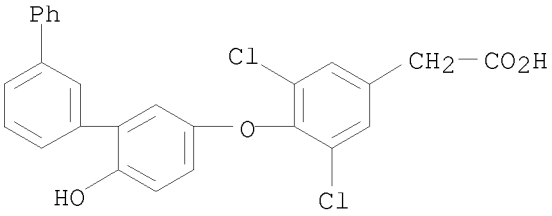
RN 725239-22-5 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(6-hydroxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



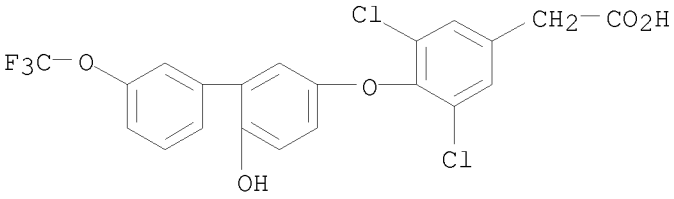
RN 725239-24-7 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[[6-hydroxy-2'-(trifluoromethyl)[1,1'-biphenyl]-3-yl]oxy]- (CA INDEX NAME)



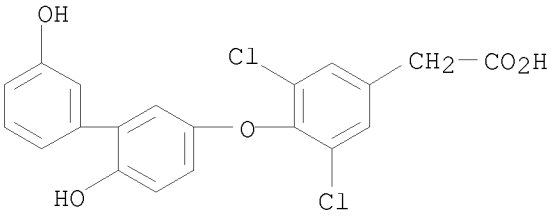
RN 725239-34-9 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(6-hydroxy[1,1':3',1''-terphenyl]-3-yl)oxy]- (CA INDEX NAME)



RN 725239-39-4 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[[6-hydroxy-3'-(trifluoromethoxy)[1,1'-biphenyl]-3-yl]oxy]- (CA INDEX NAME)



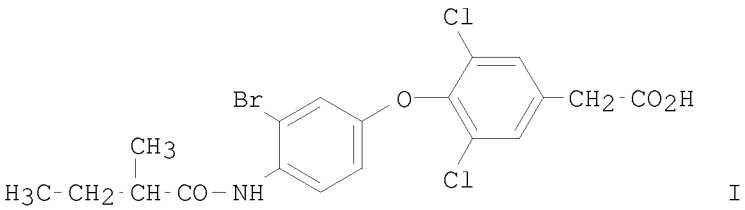
RN 725239-43-0 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(3',6-dihydroxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:16586 CAPLUS
DOCUMENT NUMBER: 144:205141
TITLE: Thyroid receptor ligands. Part 4: 4'-amido bioisosteric ligands selective for the thyroid hormone receptor beta
AUTHOR(S): Li, Yi-Lin; Litten, Chris; Koehler, Konrad F.; Mellstroem, Karin; Garg, Neeraj; Garcia Collazo, Ana Maria; Faernegard, Mathias; Grynfarb, Marlena; Husman, Bolette; Sandberg, Johnny; Malm, Johan
CORPORATE SOURCE: Karo Bio AB, Huddinge, S-141 57, Swed.
SOURCE: Bioorg. Med. Chem. Lett. (2006), 16(4), 884-886
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 144:205141
GI



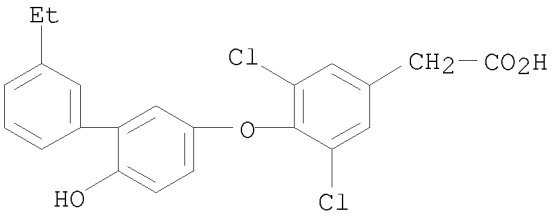
I

AB Based on the examination of the x-ray crystallog. structures of the LBD of TRα and TRβ in complex with KB-141 (2), a number of novel 4'-hydroxy bioisosteric thyromimetics were prepared Optimal affinity and β-selectivity (33 times), was found with a medium-sized alkyl-substituted amido group; iso-Bu (I). It can be concluded that bioisosteric replacements of the 4'-hydroxy position represent a new promising class of TRβ-selective synthetic thyromimetics.

IT 725239-30-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of 4'-amido bioisosteric ligands selective for thyroid hormone receptor β and thyromimetic activity)

RN 725239-30-5 CAPLUS

CN Benzeneacetic acid, 3,5-dichloro-4-[(3'-ethyl-6-hydroxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



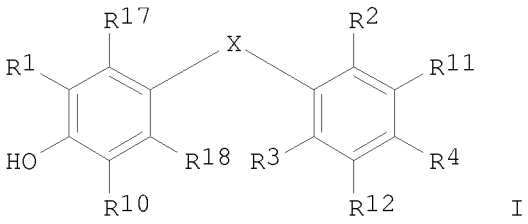
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:927006 CAPLUS
DOCUMENT NUMBER: 141:395288
TITLE: New [3,5-dihalo-4-(4-hydroxyphenoxy)phenyl]acetic acid derivatives useful as thyroid receptor ligands, and their preparation, pharmaceutical compositions, and methods of use
INVENTOR(S): Ryono, Dennis E.; Hangeland, Jon J.; Friends, Todd J.; Dejneka, Tamara; Devasthale, Pratik; Caringal, Yolanda V.; Zhang, Minsheng; Doweyko, Arthur M. P.; Malm,

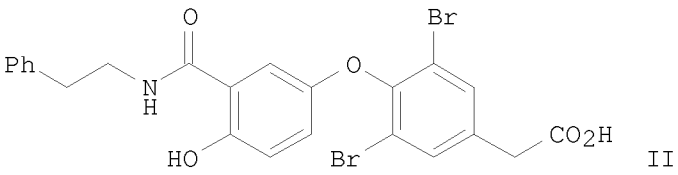
Johan; Sanin, Andrei
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004093799	A2	20041104	WO 2004-US11883	20040416
WO 2004093799	A3	20050224		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 20050004184	A1	20050106	US 2004-826100	20040415

PRIORITY APPLN. INFO.: US 2003-463774P P 20030418
OTHER SOURCE(S): MARPAT 141:395288
GI



I



II

AB Thyroid receptor ligands are provided which have the general formula I [wherein: R1 = (un)substituted CONR5R6, CH2NR5R6, NR5COR6, OR7, R8, 4-R9-4,5-dihydrooxazol-2-yl; R2, R3 = H, halo, C1-4 alkyl or C3-5 cycloalkyl, provided that at least 1 of R2 and R3 ≠ H; R4 =

(CH2)nR13 or (CH2)nCONR16CR13R14R15; R5, R6 = H, (hetero)aryl, (cyclo)alkyl, or (hetero)aralkyl; R7 = (hetero)aryl, alkyl, or (hetero)aralkyl; R8 = (hetero)aryl or cycloalkyl; R9 = R7 or H; R10 = H, halo, cyano, or alkyl; R11, R12 = H, halo, alkoxy, OH, cyano, or alkyl; R13 = COOH and esters, phosphonic and phosphinic acid and esters, sulfonic acid, tetrazole, hydroxamic acid, thiazolidinedione, acylsulfonamide, or other carboxylic acid surrogates; R14, R15 = H, alkyl; or R14R15 = (CH2)2-5, forming 3- to 6-membered cycloalkyl rings; R16 = H or C1-4 alkyl; R17 and R18 = H, halo, or alkyl; n = 0-4; X = O, S, S(O)2, S(O), Se, CO, NH, or CH2]. In addition, a method is provided for preventing, inhibiting or treating diseases or disorders associated with metabolism dysfunction, or which are dependent upon the expression of, a T3 regulated gene, wherein a compound I is administered therapeutically. Claims cover the above, as well as pharmaceutical compns. containing I, and methods of coadministration of I with other compds., particularly certain antidiabetic agents. Compds. I include selective agonists, partial agonists, antagonists, and partial antagonists of thyroid receptors (no data). Approx. 168 compds. were prepared For instance, Me (3,5-dibromo-4-hydroxyphenyl)acetate underwent O-arylation with (4-MeOC6H4)2I+ BF4-, and the resultant 4-methoxyphenyl ether derivative underwent a sequence of: (1) formylation in the 3-position, (2) O-demethylation, (3) oxidation of the aldehyde to an acid, (4) amidation of the acid, and (5) alkaline saponification of the ester, to give title compound II.

IT 725239-22-5P 725239-24-7P 725239-26-9P
725239-28-1P 725239-30-5P 725239-32-7P
725239-34-9P 725239-35-0P 725239-37-2P
725239-39-4P 725239-41-8P 725239-43-0P
725239-45-2P 788823-54-1P 788823-55-2P
788823-56-3P 788823-57-4P 788823-58-5P
788823-59-6P 788823-60-9P 788823-61-0P
788823-62-1P 788823-63-2P 788823-64-3P
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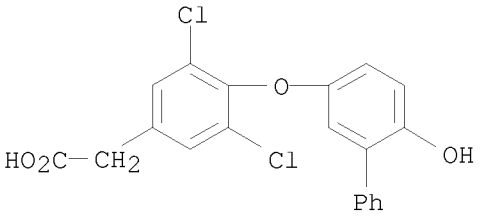
788823-68-7P 788823-69-8P 788823-70-1P
788823-71-2P 788823-72-3P 788823-73-4P
788823-74-5P 788823-75-6P 788823-76-7P
788823-77-8P 788823-78-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of [dihalo(hydroxyphenoxy)phenyl]acetic acid derivs. as thyroid receptor ligands)

RN 725239-22-5 CAPLUS

CN Benzeneacetic acid, 3,5-dichloro-4-[(6-hydroxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



RN 725239-24-7 CAPLUS
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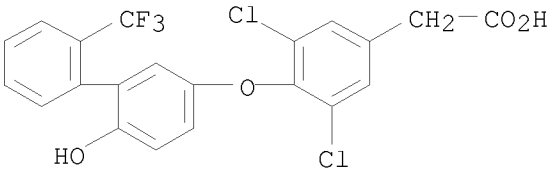

RN 725239-26-9 CAPLUS
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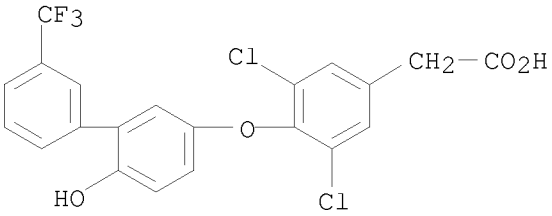
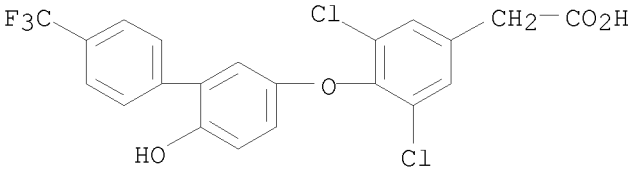


RN 725239-28-1 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[[6-hydroxy-4'-(trifluoromethyl)[1,1'-biphenyl]-3-yl]oxy]- (CA INDEX NAME)



RN 725239-30-5 CAPLUS
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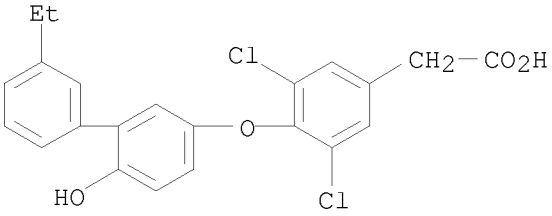
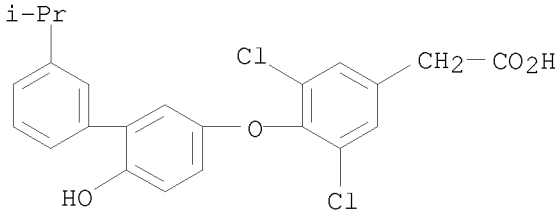


RN 725239-32-7 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[[6-hydroxy-3'-(1-methylethyl)[1,1'-biphenyl]-3-yl]oxy]- (CA INDEX NAME)



RN 725239-34-9 CAPLUS
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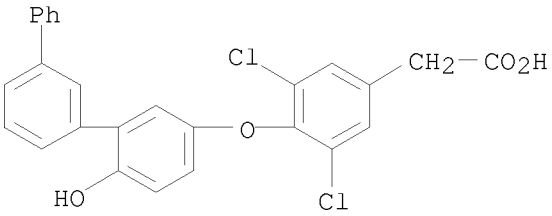
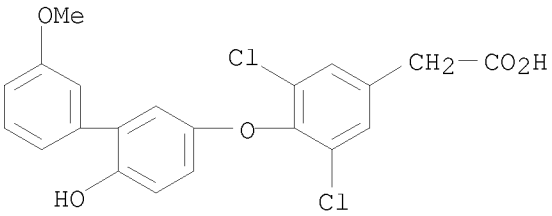
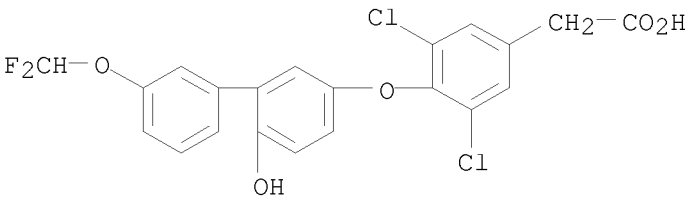


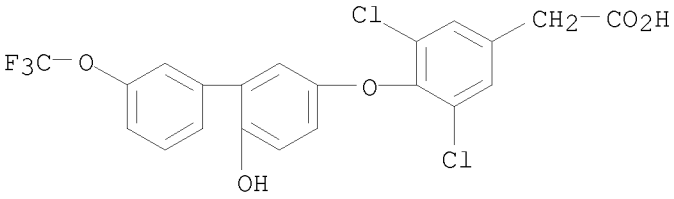
RN 725239-35-0 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(6-hydroxy-3'-methoxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



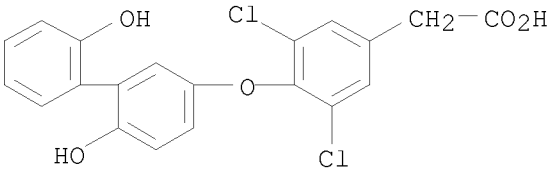
RN 725239-37-2 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[[3'-(difluoromethoxy)-6-hydroxy[1,1'-biphenyl]-3-yl]oxy]- (CA INDEX NAME)



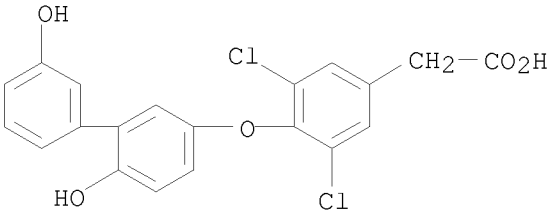
RN 725239-39-4 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[[6-hydroxy-3'-(trifluoromethoxy)[1,1'-biphenyl]-3-yl]oxy]- (CA INDEX NAME)



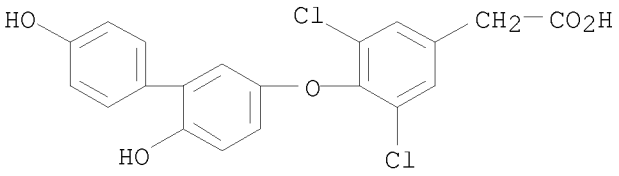
RN 725239-41-8 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(2',6-dihydroxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



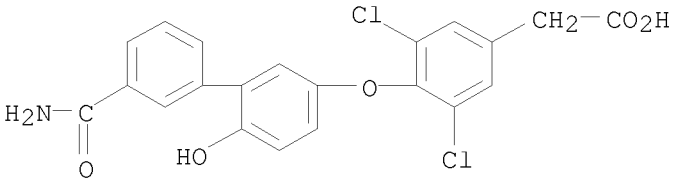
RN 725239-43-0 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(3',6-dihydroxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



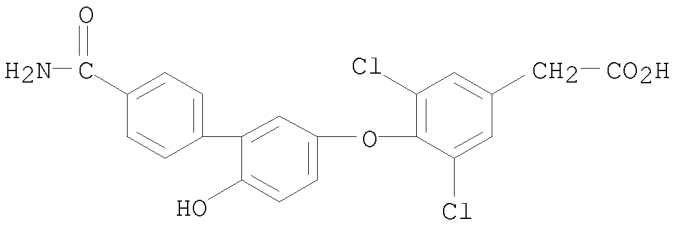
RN 725239-45-2 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(4',6-dihydroxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



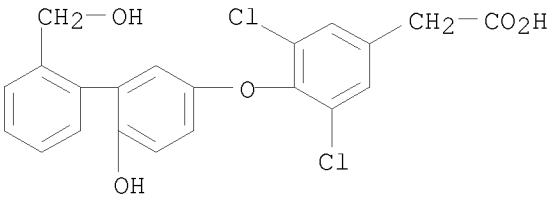
RN 788823-54-1 CAPLUS
CN Benzeneacetic acid, 4-[[3'-(aminocarbonyl)-6-hydroxy[1,1'-biphenyl]-3-yl]oxy]-3,5-dichloro- (CA INDEX NAME)



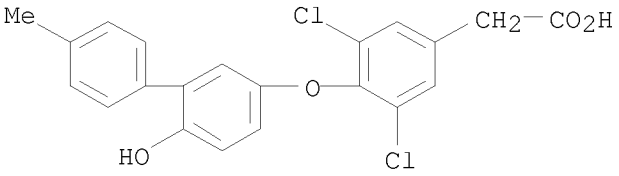
RN 788823-55-2 CAPLUS
CN Benzeneacetic acid, 4-[[4'-(aminocarbonyl)-6-hydroxy[1,1'-biphenyl]-3-yl]oxy]-3,5-dichloro- (CA INDEX NAME)



RN 788823-56-3 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[[6-hydroxy-2'-(hydroxymethyl)[1,1'-biphenyl]-3-yl]oxy]- (CA INDEX NAME)



RN 788823-57-4 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(6-hydroxy-4'-methyl[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



RN 788823-58-5 CAPLUS
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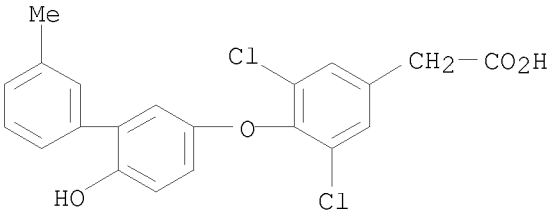

RN 788823-59-6 CAPLUS
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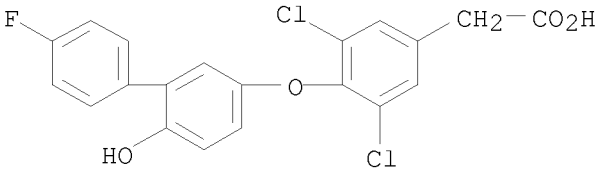
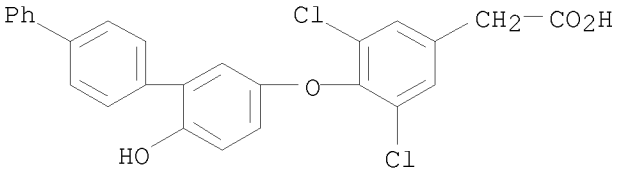


RN 788823-60-9 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(6-hydroxy[1,1':4',1''-terphenyl]-3-yl)oxy]- (9CI) (CA INDEX NAME)



RN 788823-61-0 CAPLUS
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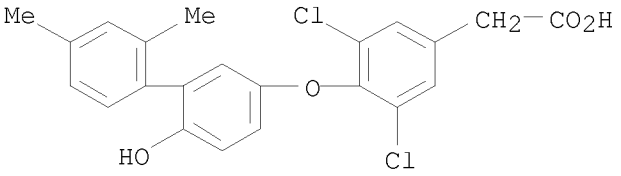

RN 788823-62-1 CAPLUS
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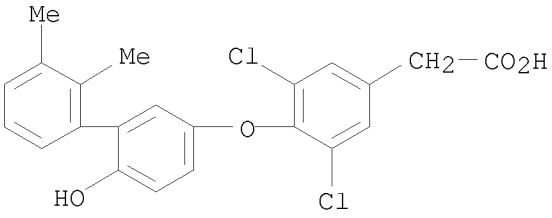
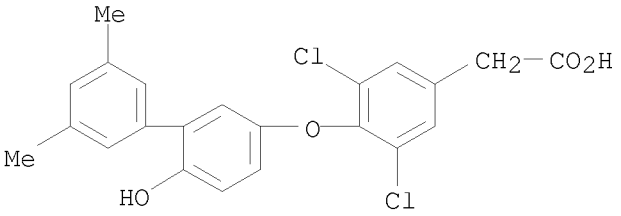
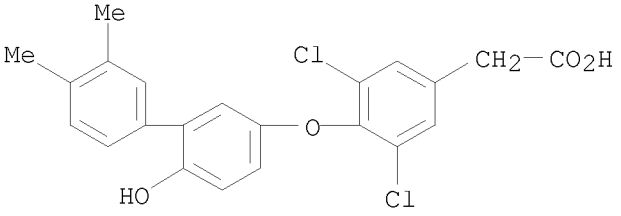


RN 788823-63-2 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(6-hydroxy-3',5'-dimethyl[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



RN 788823-64-3 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(6-hydroxy-3',4'-dimethyl[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



RN 788823-65-4 CAPLUS
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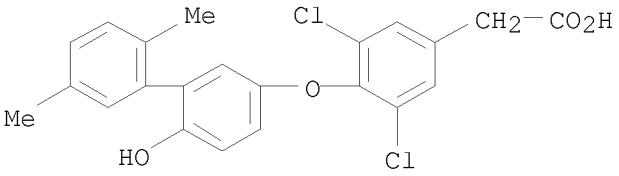
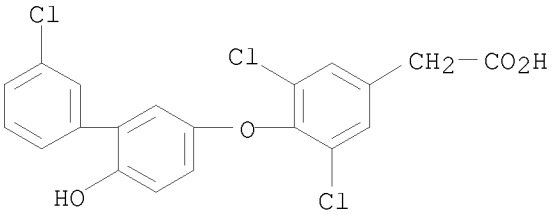
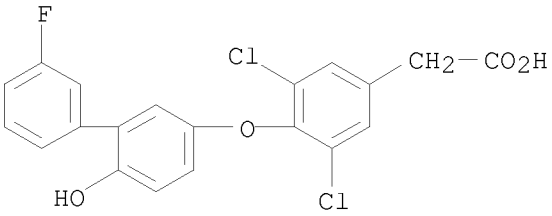


RN 788823-66-5 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(3'-chloro-6-hydroxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



RN 788823-67-6 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(3'-fluoro-6-hydroxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



RN 788823-68-7 CAPLUS
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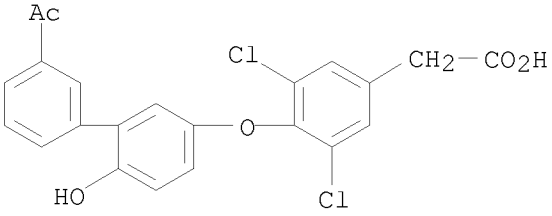

RN 788823-69-8 CAPLUS

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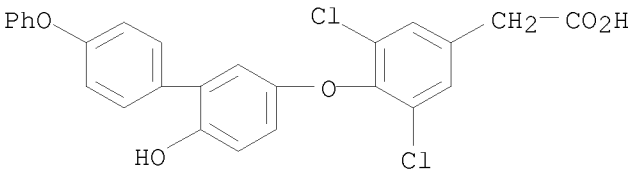

RN 788823-70-1 CAPLUS
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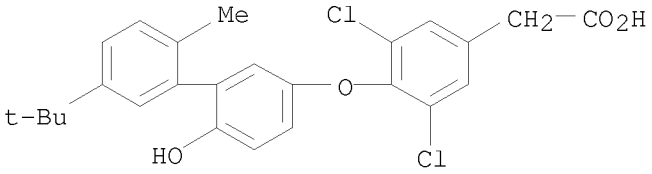
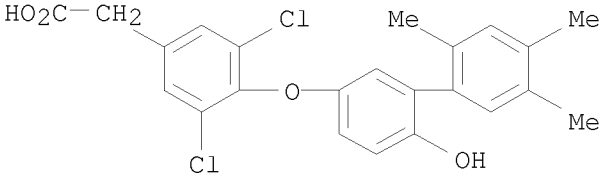
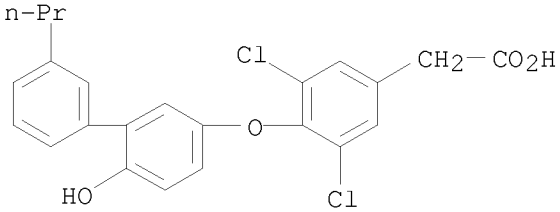


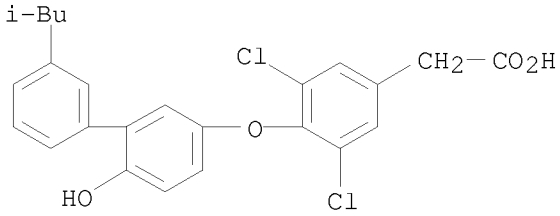
RN 788823-71-2 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(6-hydroxy-2',4',5'-trimethyl[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



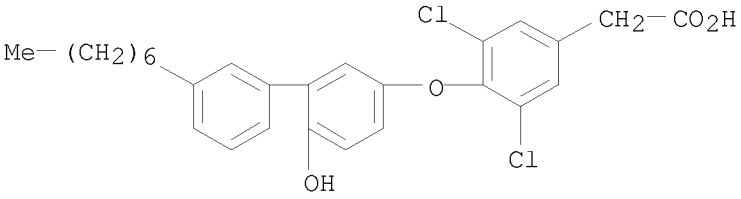
RN 788823-72-3 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(6-hydroxy-3'-propyl[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



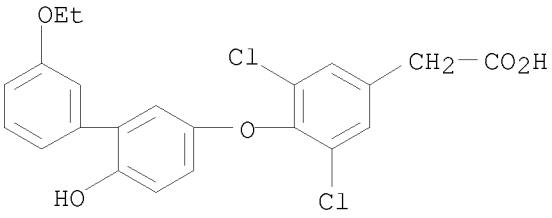
RN 788823-73-4 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[[6-hydroxy-3'-(2-methylpropyl)[1,1'-biphenyl]-3-yl]oxy]- (CA INDEX NAME)



RN 788823-74-5 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(3'-heptyl-6-hydroxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



RN 788823-75-6 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(3'-ethoxy-6-hydroxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



RN 788823-76-7 CAPLUS
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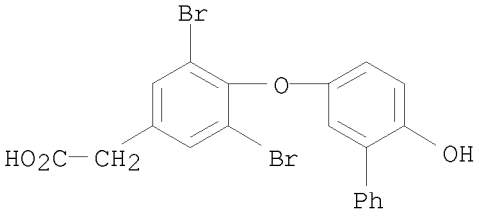
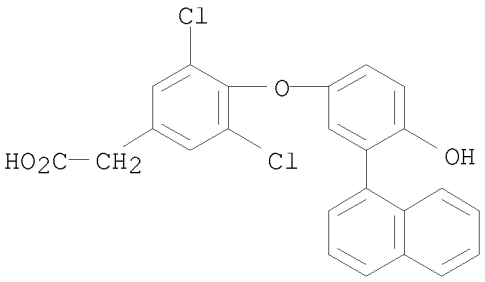
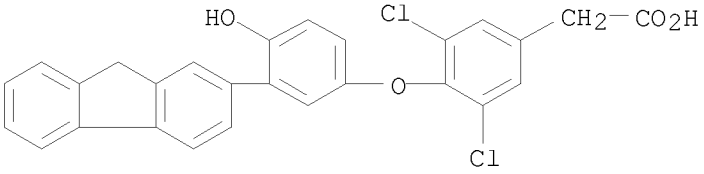


RN 788823-77-8 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[4-hydroxy-3-(1-naphthalenyl)phenoxy]- (CA INDEX NAME)



RN 788823-78-9 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[3-(9H-fluoren-2-yl)-4-hydroxyphenoxy]- (CA INDEX NAME)



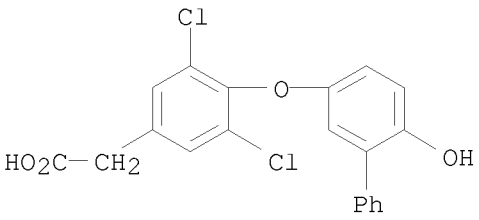
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:465510 CAPLUS
DOCUMENT NUMBER: 141:133551
TITLE: Thyroid receptor ligands. Part 2: thyromimetics with improved selectivity for the thyroid hormone receptor beta
AUTHOR(S): Hangeland, Jon J.; Doweyko, Arthur M.; Dejneka, Tamara; Friends, Todd J.; Devasthale, Pratik; Mellstrom, Karin; Sandberg, Johnny; Grynfarb, Marlena; Sack, John S.; Einspahr, Howard; Faernegardh, Mathias; Husman, Bolette; Ljunggren, Jan; Koehler, Konrad; Sheppard, Cheryl; Malm, Johan; Ryono, Denis E.
CORPORATE SOURCE: Pharmaceutical Research Institute, Bristol-Myers Squibb, Princeton, NJ, 08543, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2004), 14(13), 3549-3553
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:133551
AB A set of thyromimetics having improved selectivity for TR-β1 were prepared by replacing the 3'-iso-Pr group of 2 and 3 with substituents

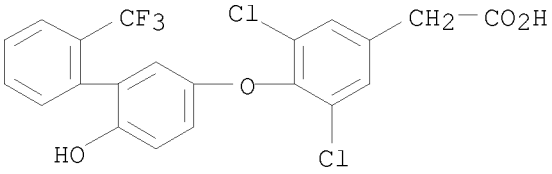
having increased steric bulk. From this limited SAR study, the most potent and selective compds. identified were derived from 2 and contained a 3'-Ph moiety bearing small hydrophobic groups meta to the biphenyl link. X-ray crystal data of 15c complexed with TR-β1 LBD shows methionine 442 to be displaced by the bulky R3' Ph Et amide side chain. Movement of this amino acid side chain provides an expanded pocket for the bulky side chain while the ligand-receptor complex retains full agonist activity.

IT 725239-22-5P 725239-24-7P 725239-26-9P
725239-28-1P 725239-30-5P 725239-32-7P
725239-34-9P 725239-35-0P 725239-37-2P
725239-39-4P 725239-41-8P 725239-43-0P
725239-45-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(structure activity relationships of thyromimetics with selectivity for thyroid hormone receptor beta)

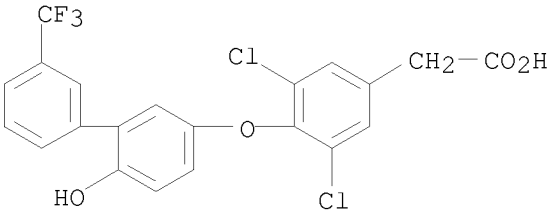
RN 725239-22-5 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(6-hydroxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



RN 725239-24-7 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[[6-hydroxy-2'-(trifluoromethyl)[1,1'-biphenyl]-3-yl]oxy]- (CA INDEX NAME)



RN 725239-26-9 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[[6-hydroxy-3'-(trifluoromethyl)[1,1'-biphenyl]-3-yl]oxy]- (CA INDEX NAME)



RN 725239-28-1 CAPLUS
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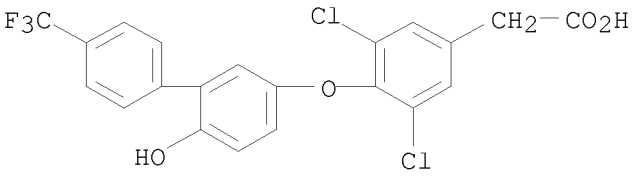
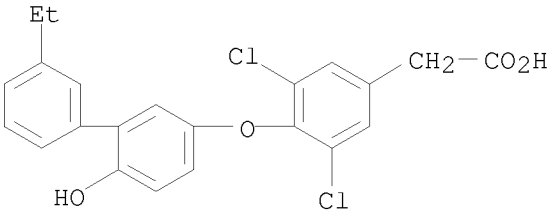
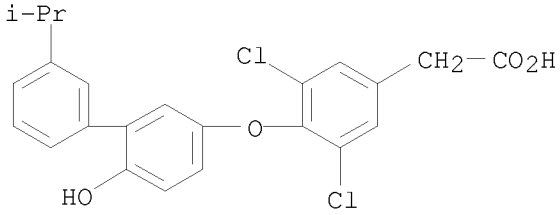


RN 725239-30-5 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(3'-ethyl-6-hydroxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



RN 725239-32-7 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[[6-hydroxy-3'-(1-methylethyl)[1,1'-biphenyl]-3-yl]oxy]- (CA INDEX NAME)



RN 725239-34-9 CAPLUS
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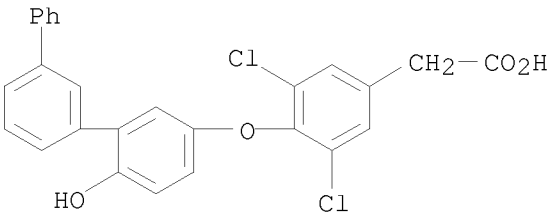

RN 725239-35-0 CAPLUS
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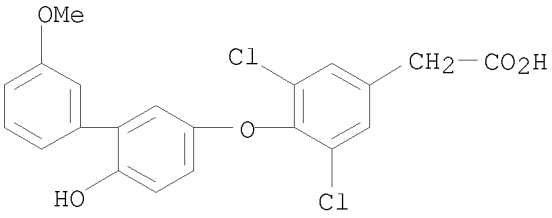
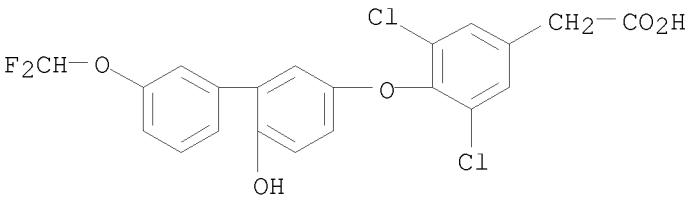
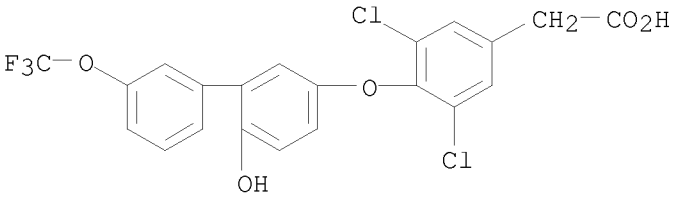


RN 725239-37-2 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[[3'-(difluoromethoxy)-6-hydroxy[1,1'-biphenyl]-3-yl]oxy]- (CA INDEX NAME)

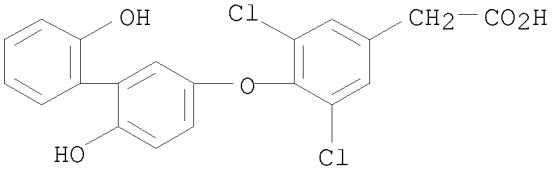


RN 725239-39-4 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[[6-hydroxy-3'-(trifluoromethoxy)[1,1'-biphenyl]-3-yl]oxy]- (CA INDEX NAME)

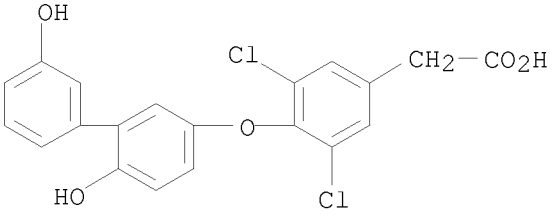


RN 725239-41-8 CAPLUS

CN Benzeneacetic acid, 3,5-dichloro-4-[(2',6-dihydroxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



RN 725239-43-0 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(3',6-dihydroxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)



RN 725239-45-2 CAPLUS
CN Benzeneacetic acid, 3,5-dichloro-4-[(4',6-dihydroxy[1,1'-biphenyl]-3-yl)oxy]- (CA INDEX NAME)